Treatment Needs in First-Episode Schizophrenia: Some Additional Perspectives

Thesis (cumulative thesis)

presented to the Faculty of Arts

of

the University of Zurich

for the Degree of Doctor of Philosophy

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Accepted in the fall semester 2012 on the

recommendation of Prof. Dr. med. Dipl.-Psych. Wulf Rössler

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Zürich, 2015

Preface

This dissertation relies on data from the EUFEST-Trial conducted by the EUFEST Study Group. I thank the members of this group, the therapists and other staff involved in the study, and all the patients who took part in the trial, for their engagement and the permission for using the data. I thank the co-authors for their contributions to the papers, namely Eske Derks for her competent methodological support and Tom Burns for his inputs. My special thanks go to Wulf Rössler for offering me the possibility to write this dissertation and for his support, and to Vladeta Ajdacic-Gross for his engaged and patient teaching of the craft of scientific work. Last but not least I thank my family and my friends and colleagues who supported me during the process of writing this dissertation.

Abstract

The three studies summarised in this cumulative dissertation deal with first-episode schizophrenia. The first episode is an especially sensitive moment shaping the course of the illness. Therefore, research on this phase is important. Treatment during the first episode should target the psychotic symptoms efficiently, but should also be as less invasive as possible. As antipsychotic medication mostly fulfils the first criterion, but less often the second criterion, it is legitimate to focus on treatments that provide relief from symptoms and eventually alternatives to continuous medication. This dissertation focuses on treatment needs (Studies 1 and 2), which encompass a broader spectrum of topics apart from medication, and deals with patients who stopped any antipsychotic medication (Study 3). All three studies were conducted using data from the EUFEST-Trial, a randomised controlled trial comparing first- versus second-generation antipsychotics in the treatment of first-episode schizophrenia. The trial encompassed in total 498 participants recruited in 13 mental health centres from different European countries and Israel. After a baseline interview, as many participants as possible were followed-up for 12 months. The longitudinal structure of the data allowed for using Latent Class Growth Analysis (LCGA), which identifies groups of persons with different courses on one outcome measure. Additionally, cox-regression and structural equation modelling were implemented. Many different findings emerged from the three studies. Among other things one study showed that especially unmet social needs persisted over the 12 months, and were often in danger of not being addressed adequately. Especially unmet needs that disappeared – instead of being met – were associated with a higher quality of life at follow-up. Moreover, there were hints that the decision

whether to continue with antipsychotic medication or not was not guided by clear rules, but rather by attitudes, local use, and “rules of thumb”. All those findings might help to improve treatment of first-episode schizophrenia, and provide ideas for further research. The dissertation closes with a critical discussion of the concept of treatment needs, the value of secondary analyses, and the generalisability of the results.

Zusammenfassung

Die vorliegende kumulative Dissertation fasst drei Studien zur ersten Episode der Schizophrenie zusammen. In der ersten manifesten schizophrenen Episode kann der Verlauf der Erkrankung positiv oder negativ beeinflusst werden, was Forschung über diese Phase besonders wichtig macht. Die professionelle Behandlung sollte in der ersten Episode sowohl auf die Reduktion der psychotischen Symptome abzielen, als auch so wenig invasiv wie möglich gestaltet sein. Antipsychotische Medikation wirkt wohl antisymptomatisch, erfüllt aber das zweite Kriterium der Nicht-Invasivität weniger deutlich. Deshalb ist es legitim, nach Behandlungsmodalitäten zu suchen welche Entlastung von Symptomen und gleichzeitig möglicherweise Alternativen zur kontinuierlichen antipsychotischen Medikation bieten.

Diese Dissertation diskutiert Behandlungsbedürfnisse der Patienten, und somit ein breites Spektrum an behandlungsrelevanten Themen (Studien 1 und 2), und stellt in der dritten Studie Patienten, welche gar keine antipsychotische Medikation mehr haben, ins Zentrum (Studie 3).

Alle drei Studien gründen auf den Daten der EUFEST-Studie, einer randomisierten kontrollierten Studie welche Antipsychotika der ersten und zweiten Generation in der Behandlung von Patienten mit einer ersten Episode der Schizophrenie vergleicht. EUFEST umfasste insgesamt 498 Studienteilnehmende, welche in 13 Behandlungszentren aus verschiedenen Europäischen Ländern und Israel rekrutiert wurden. Nach einem Erstinterview wurden die Teilnehmenden über 12 Monate weiter befragt. Die longitudinale Datenstruktur ermöglichte es, LCGA (Latent Class Growth Analysis) einzusetzen, welche verschiedene Verlaufsgruppen bezüglich eines Outcome-Masses identifizieren kann. Zusätzlich wurden die Cox-Regression und Strukturgleichungsmodelle eingesetzt.

Aus den drei Studien resultierten verschiedene interessante Befunde. Unter anderem konnte in einer Studie gezeigt werden, dass vor allem soziale unerfüllte Behandlungsbedürfnisse über 12 Monate hinweg fortbestanden, und dass diese oft nicht behandelt werden konnten. Vor allem unerfüllte Behandlungsbedürfnisse die über die Behandlungszeit hinweg verschwanden – nicht jene die behandelt wurden – waren mit einer höheren Lebensqualität am Ende der Studie assoziiert. Zudem gab es Hinweise, dass die Entscheidung, ob antipsychotische Medikation abgesetzt werden sollte, kaum durch klare Regeln begründet war. Diese Befunde können dazu beitragen, die Behandlung der Erst-Episode-Schizophrenie zu verbessern, und liefern Ideen für zukünftige Forschungsprojekte. Die Dissertation schilesst mit einer kritischen Diskussion des Konzeptes der Behandlungsbedürfnisse, dem Wert von Sekundäranalysen, und der Generalisierbarkeit der Resultate.

Index

1 Introduction

Schizophrenia is one of the disorders that result in a very high burden for the persons who are affected with. There is no possibility to heal schizophrenia up to now, even though effective treatments are available. Therefore, research which helps to understand the disorder, to develop adequate treatment methods, and to support patients to cope with the symptoms, is still urgently needed. Every little step in direction of an understanding of schizophrenia is in fact a huge advantage. The first episode of schizophrenia is an especially sensitive moment and shapes the course of the illness, since the experiences patients have with the treating therapists and institutions can be formative for their readiness to adhere to treatment in the future. In the following, some treatment concepts are summarized. For a comprehensive discussion of the topic, the interested reader is referred to the introductions of the three studies and to the large body of published research articles.

2.1 First-episode schizophrenia, treatment and treatment needs

2.1.1 Definition

First-episode schizophrenia is defined as the first occurrence of an episode of illness that fulfils the diagnostic criteria of schizophrenia spectrum disorder according to the DSM-IV or the ICD-10 diagnostic manual. This definition does not take into account the possible vagueness of boundaries at the ends of the schizophrenia spectrum; and has to be differentiated from first episode psychosis (1). The results of studies on first-episode schizophrenia can differ because of inclusion criteria. In this study, first-episode schizophrenia is defined as the first episode of DSM-IV diagnosis of

schizophrenia, schizoaffective disorder or schizophreniform disorder (2). As schizophreniform and schizoaffective disorders have better prognoses than schizophrenia, the inclusion of those diagnoses might result in better outcomes in this sample compared with samples reduced to schizophrenia alone (3, 4). The diagnosis of schizophrenia includes a time criteria specifying that signs of the illness must be present for at least 6 months. Therefore, a first episode can only be diagnosed after some time has passed. Even then, first-episode samples show higher rates of response to antipsychotic medication and remission than samples with an established illness (2). Among the first-episode patients, there are obviously more cases with a better prognosis who might benefit from different treatment strategies.

Before the exacerbation of a first episode of schizophrenia, a more or less pronounced prodromal phase occurs in most of the cases. Any intervention during this prodromal phase in turn influences the course of illness. Thus, systematic early intervention might result in more cases who do well with minimal invasive treatment options (5).

2.1.2 Treatment of first-episode schizophrenia

Antipsychotic medication is the recommended treatment method in any phase of the established illness (6, 7). But additionally, to address psychosocial functioning is considered (8) which is supposed to hinder deterioration in such functioning during the later course of the illness (9). In first-episode schizophrenia, there are some arguments against default medication: As medication often provokes severe side effects (10-14), patient's adherence is impaired and their compliance with treatment affected. Compliance and adherence is important for the later course of the illness

(15, 16). Moreover, studies constantly identify a proportion of patients who remit without medication (17, 18); their number is strongly dependent on the definition of relapse (19). Age, social competence, prognosis and number of diagnostic symptoms (18, 20) are possible predictors of response without antipsychotic medication, but results of different studies are inconsistent (20).

As there are patients who remit without antipsychotic medication, criteria are needed to decide when to continue or to discontinue medication (17). Thus, the challenge is to treat the psychotic episode efficiently, but at the same time, to use a treatment method that is as less invasive as possible. This legitimates the focus on treatment alternatives to antipsychotic medication.

2.2 Treatment needs

2.2.1 Definition

In general, the concept of treatment need is determined by recovery from illness. From the perspective of severe mental illnesses, this is reduced to the need of interventions that enhance quality of life and help the patient to cope with the symptoms and the consequences of being severely mentally ill. In this context, treatment needs are defined as prerequisites for maintaining or restoring an acceptable level of social independence and quality of life (21).

2.2.2 Psychological interventions

Next to medication targeted to reduce psychotic symptoms, patients suffering from schizophrenia have widespread treatment needs. Psychological interventions are an important component of treatment of early psychosis, even though final scientific

proof for the efficacy of those interventions is still needed (22). Psychological interventions are useful to address substance use (23), activate protective factors, or are targeted to specific symptoms or deficits (24). Cognitive approaches might improve functioning (25), among other things. Last but not least there is the need to keep physical health: Persons suffering from schizophrenia might suffer from inequalities in healthcare provision which in turn influences mortality rates (26).

3 Aims

The general aim of the secondary analyses was to add to the knowledge about treatment needs in first-episode schizophrenia using a large data set – which proved to be very useful for the discussion on first- and second-generation antipsychotics (27) - by focusing on treatment needs apart from antipsychotic medication.

The main specific aims were:

1. To gain broader insight into the longitudinal interrelation between quality of life, unmet needs, symptom severity, clinical status, and functioning by differentiating needs that are being met and needs that disappear during treatment.
2. To identify the course of needs over a 12-month period in first-episode patients compared with chronic schizophrenia patients.
3. To identify clusters of patients with different trajectories of unmet needs.
4. To determine variables that are associated with the trajectories of unmet needs.

5. To find out more about patients suffering from first episode schizophrenia but not using antipsychotic medication continuously.
6. To examine whether any useful information at all could be gained from such trials regarding the topic of non-continuous antipsychotic medication.

4 Implementation

4.1 Data and Methods

4.1.1 The EUFEST-Trial

All analyses were conducted using data from the EUFEST-Trial (2, 27), a randomised controlled trial comparing first- versus second-generation antipsychotics in the treatment of first-episode schizophrenia. The trial encompassed in total 498 participants recruited in 13 mental health centres from different European countries and Israel. Outcome of the core study was discontinuation of study drug. But all patients who did not drop out of the study were followed up with in total 9 assessments encompassing one year. A wide range of information was assessed at different visits, which allowed for studying other themes than first- versus second-generation antipsychotic medication using the EUFEST data. The three studies summarised in this dissertation focused on treatment needs and the question of antipsychotic-free treatment.

4.1.2 Treatment needs

Treatment needs are often assessed using questionnaires. This study uses the CAN (Camberwell Assessment of Need; (28)), inquiring about 22 potentially problematic

areas of living and differentiating among met need (patient has a need and this need is met by treatment), unmet need (specific need that is not met by treatment), and no need (patient does not have a need in this area of living). Using a questionnaire has the advance of yielding reliable data, also when the interviewers are not clinicians or extensively trained. But it is possible that individual needs, or needs that are especially important for first-episode patients, are missed by the a priori defined questions.

4.2 Summaries of the studies

4.2.1 Study 1

The first study aimed to identify the course of unmet needs by patients with a first episode of schizophrenia and to determine associated variables.

Baseline assessments in the EUFEST trial as well as follow-up interviews at 6 and 12 months were investigated. Latent class growth analysis was used to identify patient groups based on individual differences in the development of unmet needs. Multinomial logistic regression determined the predictors of group membership.

Four classes were identified. Three differed in their baseline levels of unmet needs while the fourth had a marked decrease in such needs. Main predictors of class membership were prognosis and depression at baseline, and the quality of life and psychosocial intervention at follow-up. Depression at follow up did not vary among classes.

Subtypes of patients with different courses of unmet needs were identified. Needs concerning social relationships were particularly persistent in subtypes who remained high in their unmet needs and who lacked additional psychosocial treatment.

4.2.2 Study 2

The interrelation between needs for care and quality of life has been described and replicated by several studies. The second study aimed to add to the understanding of longitudinal interrelations between needs for care, quality of life, and other outcome measures by analyzing a sample of patients at the onset of schizophrenia.

This study relied on the first (baseline) and the last assessment (12 months after baseline) of the EUFEST-Trial. Predictors of quality of life were determined using regression analyses. The complex longitudinal interrelations between baseline and outcome measures were tested with structural equation models.

There was a marked improvement in the total sample on all psychosocial and psychopathological measures. Needs were not definitively confirmed as a predictor of subsequent quality of life. Unmet needs changing to no needs were a stronger predictor of quality of life than unmet needs changing to met needs.

This study suggests that when studying quality of life and needs for treatment, it is crucial to differentiate whether unmet needs disappear or whether they were met, as the former has a stronger impact on quality of life.

4.2.3 Study 3

This study aimed to describe patients suffering from first-episode schizophrenia who stopped taking any antipsychotic medication, and to gain information on the predictors of successful discontinuation. Since trials comparing placebo or psychosocial intervention against antipsychotic medication raise ethical concerns, secondary analyses are particularly important in this context.

We investigated data from the European First Episode Schizophrenia Trial (EUFEST). In a first analysis, global correlates of discontinuing antipsychotic medication were identified using Cox-regression. In the second study, logistic

regression was used to determine variables associated with those patients who had stopped taking antipsychotic medication and had a favorable outcome, i.e., successful discontinuation.

Cox-regression revealed that more patients from Western European countries and Israel stopped antipsychotic medication than from Central and Eastern European countries, that relapse was associated with discontinuing, and that those persons had lower compliance and higher quality of life. Predictors of successful discontinuation differed with the outcome definition used. When a good outcome was defined as having no relapse, successful discontinuers were more often from Western European countries and Israel, had more often an abnormal ECG and higher baseline depression scores. When a good outcome was defined as having no relapse and reaching symptomatic remission, successful discontinuers had a better prognosis and better baseline social integration.

Initial depression, prognosis and social integration played an important role in predicting successful discontinuation. As decisions of therapists and patients regarding antipsychotic medication seemed to be also influenced by local treatment practice and factors other than clinical status, further studies are needed to identify and discuss basic principles of decision making.

5 Integration of results

These three studies addressed the broad spectrum of treatment needs in first-episode schizophrenia and resulted in some findings that should be considered when attempting to improve the treatment of first-episode schizophrenia and in future research. The *first study* indicated that especially unmet social needs seem in danger of not being addressed adequately, which might impair psychosocial functioning of patients in the long-term. The *second study* moderates the finding that meeting need by treatment enhances outcome quality of life (29, 30). It shows that the disappearance of unmet needs – not meeting them per se – is important for a better quality of life after 12 months. The *third study* confirms that treatment without antipsychotic medication is possible for at least some patients. But it also indicated that the decision for treatment without antipsychotic medication seems to be last but not least a question of attitude of therapists and patients.

5.1 Is treatment need a meaningful concept for research and treatment guiding in first-episode schizophrenia?

There are arguments that question the usefulness of treatment needs as a meaningful concept in research and treatment of schizophrenia (31). Regarding first-episode schizophrenia, there is no discussion on this topic up to now. The following pro arguments can be inferred from the present studies: First of all, the concept of need accounted for the wants and wishes of the individual patient. This is a pro argument because it leads the focus not only on medication but also on other areas of patient's life, e.g. social needs, which might be of importance for at least some

patients. As needs can differ from patient to patient, research on needs should always discern different groups of patients with different combinations of needs. Keeping the diversity of needs in mind will also lead idea finding in research.

On the more negative argumentative side are the inconsistent interrelations of treatment needs with other well-established outcome measures in first-episode schizophrenia, especially psychopathology and quality of life. On the one hand, this could mean that treatment need measures another dimension of outcome than the other measures. But, on the other hand, it might be possible that the concept of need is not a valid outcome measure in first episode schizophrenia. Last but not least, the difference between disappearing needs and needs that are being met remained unclear. Here, further research is needed to answer those questions and to enable an unequivocal decision regarding the benefit of measuring treatment need in first-episode schizophrenia.

5.2 What can be learned from secondary analyses of RCT's on antipsychotic medication?

The secondary analyses of the EUFEST-Study data yielded findings that provided interesting ideas for research and treatment. But as secondary analyses are explorative by design, and findings from such studies always need confirmation by experimental research, the question remains whether the results are important enough to legitimate the amount of work such analyses afford.

Some pro arguments are the following:

- First, it was also a large amount of work to collect the data of the EUFEST-Study. The EUFEST-Trial encompassed a remarkable, very uniform sample of first-episode patients treated in different European mental health centres, and used a broad collection of measures of different aspects of the illness. Analysing as many of those concepts assessed, resulting in a broad spectrum of findings, values the participant's effort by making the best of it.
- Another topic is whether the trial's focus on medication limits the validity of results not concerning medication. On the one hand it does, because the study has been designed to test this topic, and when studying other questions one is often confronted with limited capacity of the study design. On the other hand, other themes are not subjected to biases generated by participating in a (non-double-blinded) study. Moreover, the researcher is not prejudiced regarding the results of secondary analyses because he is in the debt of the sponsors who funded the study.

5.3 Outlook

An important conclusion from the three secondary analyses is that treatment needs is a very complex outcome measure with manifold associations and equivocal interrelations with psychopathology and standard antipsychotic medication. Moreover, as two of the analyses showed, to identify patients with different courses of outcomes is a very useful procedure in research that aims to generate hypotheses. To close with, my most important point is to encourage research on the whole spectrum of treatment needs and treatment options in first-episode schizophrenia, as this is, to my opinion, a good way to support practitioners to be responsive to the

individual person of the patient, and to find the treatment mode which supports him/her best on her/his way towards health.

5.4 Evaluation of the relevance of the findings

Any relevance of findings depends strongly on the generalizability of the results. The EUFEST-Trial collected a large sample of patients coming from different mental health centres in Europe and Israel. The sample is not representative concerning the selection of centres and patients. Therefore, it gives a good overview over the situation in Europe, but strictly speaking, results cannot be generalized to all first-episode patients. Another critical point is the definition of first-episode schizophrenia. As described in paragraph 1.1.1, the definition is not unequivocal. Moreover, patients were included when the onset of positive symptoms was no longer than two years ago. Within two years, it is possible that more than one episode of schizophrenia has occurred. Despite the large total sample, each of the three analyses struggled with marginal sample sizes. Therefore, statistical models were not very stable, and it is possible that the effects of some predictors were over- and effects of others underestimated. The results clearly need to be confirmed by other studies.

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Appendix

I Study 1: Unmet needs in patients with first-episode schizophrenia: a longitudinal perspective

Published in: Psychological Medicine, 2012 Jul;42(7):1461-73.

doi: 10.1017/S0033291711002406. Epub 2011 Nov 21.

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Abstract

Background:

This study aimed to identify the course of unmet needs by patients with a first episode of schizophrenia and to determine associated variables.

Methods:

We investigated baseline assessments in the EUFEST trial as well as follow-up interviews at 6 and 12 months. Latent class growth analysis was used to identify patient groups based on individual differences in the development of unmet needs. Multinomial logistic regression determined the predictors of group membership.

Results:

Four classes were identified. Three differed in their baseline levels of unmet needs while the fourth had a marked decrease in such needs. Main predictors of class membership were prognosis and depression at baseline, and the quality of life and psychosocial intervention at follow-up. Depression at follow up did not vary among classes.

Conclusions:

We identified subtypes of patients with different courses of unmet needs. Prognosis of clinical improvement was a better predictor for the decline in unmet needs than was psychopathology. Needs concerning social relationships were particularly persistent in subtypes who remained high in their unmet needs and who lacked additional psychosocial treatment.

II Study 2: The interrelation of needs and quality of life in first-episode schizophrenia

Published in: European Archives of Psychiatry and Clinical Neurosciences. 2012 Apr;262(3):207-16.

doi: 10.1007/s00406-011-0275-6. Epub 2011 Nov 24.

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Abstract

Background:

The interrelation between needs for care and quality of life has been described and replicated by several studies. The present work aims to add to the understanding of longitudinal interrelations between needs for care, quality of life, and other outcome measures by analyzing a sample of patients at the onset of schizophrenia.

Methods:

This study relied on data from the EUFEST trial, designed to compare first- and second-generation antipsychotics during one year. At baseline, 498 patients have been included. The first (baseline) and the last assessment (12 months after baseline) were used for the analyses. Predictors of quality of life were determined using regression analyses. We tested the complex longitudinal interrelations between baseline and outcome measures with structural equation models.

Results:

Unmet needs were not definitively confirmed as a predictor of subsequent quality of life, unless unmet needs changing to no needs were separated from unmet needs changing to met needs. Each unmet need that changed to no need enhanced quality of life (mean score 1 - 7) by 0.136 scale points.

Conclusions:

This study suggests that when studying quality of life and needs for treatment, it is crucial to differentiate whether unmet needs disappeared or whether they were met, as the former has a stronger impact on quality of life.

III Study 3: Discontinuation of antipsychotic medication: Predictors and outcomes in the EUFEST trial

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Abstract

Background:

This study aimed to describe patients suffering from first-episode schizophrenia who stopped taking any antipsychotic medication, and to gain information on the predictors of successful discontinuation. Since trials comparing placebo or psychosocial intervention against antipsychotic medication raise ethical concerns, secondary analyses are particularly important in this context.

Methods:

We investigated data from the European First Episode Schizophrenia Trial (EUFEST). In a first analysis, global correlates of discontinuing antipsychotic medication were identified using Cox-regression. In the second study, logistic regression was used to determine variables associated with those patients who had stopped taking antipsychotic medication and had a favorable outcome, i.e., successful discontinuation.

Results:

Cox-regression revealed that more patients from Western European countries and Israel stopped antipsychotic medication than from Central and Eastern European countries, that relapse was associated with discontinuing, and that those persons had lower compliance and higher quality of life. Predictors of successful discontinuation differed with the outcome definition used. When a good outcome was defined as having no relapse, successful discontinuers were more often from Western European countries and Israel, had more often an abnormal ECG and higher baseline depression scores. When a good outcome was defined as having no

relapse and reaching symptomatic remission, successful discontinuers had a better prognosis and better baseline social integration.

Conclusions:

Initial depression, prognosis and social integration played an important role in predicting successful discontinuation. As decisions of therapists and patients regarding antipsychotic medication seemed to be also influenced by local treatment practice and factors other than clinical status, further studies are needed to identify and discuss basic principles of decision making.

Introduction

Antipsychotic medication is the state of the art in treating first-episode schizophrenia (1). However, the potentially serious side effects of first- and second-generation antipsychotics (2-6), and findings identifying a small proportion of first-episode patients who do well with psychosocial intervention alone (7) serve as a basis for a discussion of the necessity of antipsychotic medication in these patients (for a comprehensive overview see (8)). In the long-term, about one third of patients may not need antipsychotics continuously (9). Moreover, adherence in first-episode patients is poor (10-12). Therefore, strategies to reduce medication without putting the benefits of antipsychotics at stake have been suggested. Some authors introduced approaches that include - more or less scheduled - gaps of days or weeks where no antipsychotic drugs are given (e.g. non-continuous dosing, “drug holidays”) (13). Non-continuous antipsychotic dosing is supposed to maintain antipsychotic efficacy and decrease the risk of side effects compared with continuous dosing (13). But for most of the patients, with longer gaps relapse- and rehospitalisation rates increase (14). Other authors advocate alternative treatment strategies for at least a subgroup of patients who show an antipsychotic-free treatment response (8, 15-17). For this approach, it would be of utmost importance to be able to identify patients with a high likelihood of an antipsychotic-free treatment response as early as possible. This might be possible by a stepwise refinement of predictive knowledge from successive research studies. Firstly, a thorough review of existing studies dealing with the topic and additional secondary analyses of existing data sets are needed. Once reasonably reliable predictive factors have been identified, randomized controlled studies should be considered. The same holds true when planning to introduce medication gaps (non-continuous dosing). Unfortunately,

predictors of successful discontinuation are largely unknown (14), as are predictors of an entirely antipsychotic-free positive treatment response (8). This study aimed to study predictors of successful discontinuation (i.e. having a favourable outcome despite not continuing to take antipsychotic medication), and to add to the knowledge on the circumstances associated with the discontinuation of antipsychotic medication in first-episode psychosis.

As cited above, there are relevant arguments for the potential benefits and feasibility of non-continuous dosing and, for certain patients, treatment without antipsychotic medication. But studies that address these topics are rare because they are ethically critical (7, 18, 19). Since medication is necessary in most instances, one would not risk withholding antipsychotic medication. Naturalistic studies and secondary analyses of antipsychotic medication trials may shed more light on this issue. The European First Episode Schizophrenia Trial (EUFEST) is well suited for such secondary analyses because all patients were started on antipsychotic medication at baseline, and because patients were followed up even if they did not continue to take study medication. The study was designed as a pragmatic clinical trial in order to reflect everyday clinical practice as much as possible. In addition, EUFEST comprises a remarkably large and homogenous sample of patients (20).

The aim of the present paper is to provide more information about patients suffering from first-episode schizophrenia who discontinue antipsychotic medication. Study 1 attempts to identify variables associated with discontinuing antipsychotic medication and study 2 aims to identify predictors of successful discontinuation.

Methods

Database

This study is based on data from the European First Episode Schizophrenia Trial (EUFEST) (20, 21), in which four second-generation antipsychotics (amisulpride, olanzapine, quetiapine and ziprasidone) were compared to treatment with a low dose of haloperidol (21). Details of the study design have been previously reported (20, 21). The main outcome measure was loss of retention (LOR) in the study after one year or, in other words, the comparative proportion of patients who stayed on the antipsychotics they were initially randomized to. Patients who met LOR criteria were nevertheless followed up over the one year observation period and eventual switches to other antipsychotics were recorded. In contrast to the primary EUFEST report, *the focus of the present paper is on <u>any</u> antipsychotic, not on the original study medication, and the outcome measure is the discontinuation of <u>all</u> antipsychotic medications.* From the various additional outcome measures assessed in EUFEST, psychosocial and psychiatric symptom measures, electrocardiogram (ECG), functioning, quality of life, and Clinical Global Impression were used for the purpose of the present analyses (see below).

Sample

Fifty mental health centres in 13 European countries and Israel were selected for participation. Altogether, 1047 patients were screened for eligibility between December 2002 and January 2006. Inclusion criteria were ages 18 to 40 years; a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder; onset of positive symptoms dating back two years at most; use of antipsychotic drugs for at most two weeks in the previous year not more than total of

six weeks at any time; and no known intolerance or contraindication for one of the study drugs. Diagnoses were confirmed by the International Neuropsychiatric Interview (MINI plus) (22). In all, 498 patients gave informed consent and were randomly assigned to five treatment groups. The study protocol was evaluated by local ethics committees or review boards according to country-specific laws.

Attrition rates

Of the 1047 patients initially assessed for eligibility, 498 were included and randomized to one of the study drugs. 291 (58.4%) continued and 207 (41.6%) discontinued the study drug. Of those who continued, 198 (68.0%) patients completed the 12-month follow-up, 194 of which could be included in the present analyses. Of those who discontinued study drug, 144 (69.6%) completed the full follow-up, 13 of them were excluded from the analyses because of missing data. The 80 patients who switched to or added another antipsychotic agent, or changed dose of study medication, were added to the 194 patients who continued study drug, together building the sample of 274 “continuers” (Figure 1). 51 patients were identified who discontinued any antipsychotic medication, building the sample of “discontinuers” (Figure 1). The sample used in the present analyses thus comprised 325 patients (274 “continuers” and 51 “discontinuers”) (Figure 1).

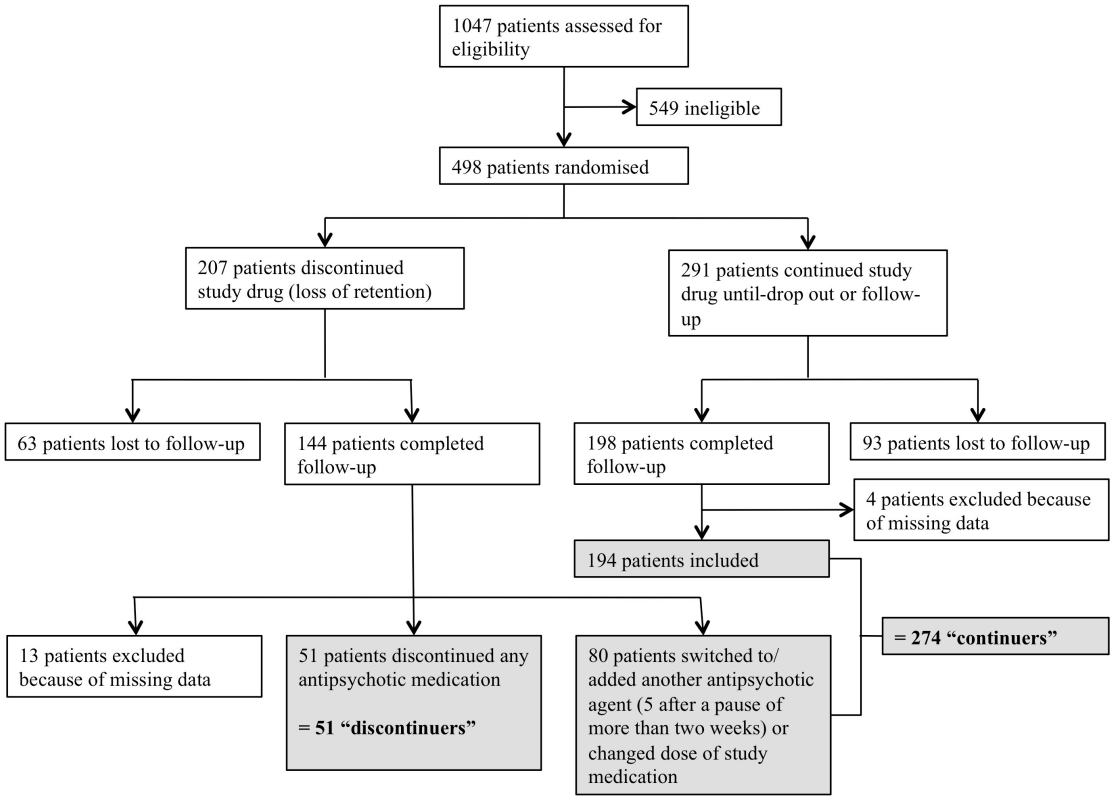

Figure 1: Flow chart illustrating the selection of the sample of the EUFEST-Trial and the sample used for the present analyses. For studies 1 and 2, the subsamples in the shaded boxes were used.

Study 1

Study 1 is close to the main EUFEST-paper (21) regarding the methods used. The difference is that the present study aimed to identify the correlates of stopping any antipsychotic medication, while the primary EUFEST-paper focused on the antipsychotic medication patients were randomly assigned to at study baseline. To this end, patients who stopped any antipsychotic medication and did not recommence during the 12-months trial duration were identified. All patients who discontinued medication had several follow-up interviews (Visits 2-9), analogous to the patients who continued on study medication. All medication use was assessed at

each visit by recording the dates of beginning and ending. This information allowed for calculating the exact time-span a patient spent on treatment, which was used as a dependent variable in a Cox-regression model. Cox-regression uses the hazard-function to examine the survival time depending on external influences. Therein it is possible to define time-dependent covariates. All independent variables listed below (see “independent variables”) were used in this model. Repeatedly measured independent variables were integrated in the model as segmented time-dependent covariates. Missing values on independent variables were replaced by the mean of the two values of the previous and following visit. When two or more consecutive values were missing, no replacement was made, and the respective cases were excluded for study 1. This applied to nine patients of the basic sample (N = 325). The “backstep Wald” procedure was used to identify most relevant covariates (independent variables). Cox-regression models were calculated with SPSS (PASW Statistics 18.0).

Study 2

In the second study, we were interested in the characteristics of patients who were successful “discontinuers”. Two definitions of success, i.e. a favourable outcome, were used: A wider one, having had no clinical relapse, and a narrower one, being a combination of no relapse and symptomatic remission, as defined by Andreasen et al. (23). The group of successful discontinuers was compared a) to the whole rest of the basic sample of 325, thus identifying successful discontinuers from all other patients, and b) to the patients who stopped antipsychotic medication and did not have a favourable outcome, thus differentiating between successful and unsuccessful discontinuers. Logistic regression was used for all the comparisons described above. Using bivariate regressions, associated baseline variables were

selected from the predictors described below (see section “independent variables”) on the basis of their significance ($P<0.05$). All bivariately significant variables were entered into one regression model, and the strongest predictors were determined with the FSTEP procedure (several predictors) or the ENTER procedure (only one predictor) using SPSS (PASW Statistics 18.0).

Independent Variables

Several measures were selected as predictors: gender, age, country, years of education, electrocardiogram (ECG) (ECG is relevant because many antipsychotics have cardiac side effects, thus patients with an abnormal baseline ECG have fewer possibilities to switch to other antipsychotic agents, e.g. should avoid typical antipsychotics and ziprasidone), prognosis (a six-point scale ranging from 1=best to 6=bad), remission (PANSS items according to (23), see also (24)), relapses, compliance (Hayward scale (25)), positive and negative symptoms (PANSS, Positive And Negative Syndrome Scale (26)), anxiety (from the PANSS), depression (CDSS, Calgary Depression Scale for Schizophrenia (27)), GAF (Global Assessment of Functioning (28)), CGI (Clinical Global Impression (29)), unmet needs (CAN, (30)), quality of life (MANSA, Manchester Short Assessment of Quality of Life (31)), and a proxy for social integration at baseline using items from the MANSA (satisfaction with friendships, family, sex life, cohabitants) and the CAN (met or unmet need regarding company, intimate relationship, sexual expression).

For study 2, a combined outcome measure was determined via two criteria:

a) having had any relapse during the study (yes/no), and b) symptomatic remission at 12-months follow-up (PANSS items according to Andreasen et al. (23), see also (24)).

The 14 participating countries were clustered into two regions: Western European (The Netherlands, Belgium, France, Switzerland, Austria, Germany, Sweden, Spain, and Italy) and Eastern and Central European (Bulgaria, Poland, Romania, and Czech Republic). Because only a few patients were from Israel, that country was added to the Western European category to control for cell sizes and confidence intervals.

Results

Study 1

Study 1 focused on the correlates of discontinuing any antipsychotic medication. Of the 325 patients included in the basic sample, 51 discontinued antipsychotic medication completely, 80 switched from the original study medication to another antipsychotic, and 194 did not change the drug they were randomised to at baseline (Figure 1). Time until complete discontinuation of the 51 patients was used as the dependent variable in the Cox-regression. Patients who continued the study drug or switched to another agent were defined as censored (N = 80 + 194 = 273, see Figure 1). Significant correlates of stopping antipsychotic medication were: Coming from Western Europe / Israel, lower compliance, relapse, and a better quality of life. Variables in the final model that were not significant were abnormal ECG and better prognosis (Table 1). A cross-tabulation revealed that abnormal ECG was only associated with stopping in Eastern- and Central-European countries (results not shown but available on request).

Table 1: Results of Cox-Regression. Dependent variable = duration of phase with any antipsychotic medication. Displayed are predictors included in step 13 using the backstep method with the Wald-Criteria (N = 316, N(event) = 50, N(censored) = 266; PIN = 0.05, POUT = 0.10).

	B	SE	Wald	Df	P	Exp(B)
Region (WE = 1 EE = -1)	0.399	0.152	6.894	1	0.009	1.491
Compliance (high = better)	-0.436	0.087	25.319	1	0.000	0.647
ECG V1 (1 = norm, -1 = abn)	-0.301	0.181	2.776	1	0.096	0.740
Prognosis V1 (high = worse)	-0.212	0.120	3.127	1	0.077	0.809
Relapse (1 = no yes = -1)	-0.482	0.229	4.427	1	0.035	0.618
Quality of life	0.390	0.178	4.780	1	0.029	1.477

Study 2

Relationship between (dis-)continuation of antipsychotics and outcome

In the second study, we focused on the characteristics of patients who discontinued antipsychotic medication and had a favourable outcome, i.e. successful "discontinuers". Of the 51 participants who stopped any antipsychotic drug as defined in study 1, 12 (23.5%) had at least one relapse, while 39 (76.5%) had no relapse; considering a more stringent definition of outcome (no relapse and symptomatic remission), 18 (35.3%) had a good, and 33 (64.7%) not a good outcome (Table 2). Table 2 also illustrates the different reference groups used in the analyses of Study 2.

Table 2: Comparison groups used in Study 2. "No medication – good outcome" is the target group that was compared to two different reference groups, A and B (rows), using two definitions of success (columns). Depicted are numbers of patients in the respective cells.

	No relapse	No relapse AND remission
No medication / good outcome	39	18
Ref. group A: rest of basic sample	281	304
Ref. group B: not good outcome, no medication	12	33

Outcome in the wider definition did not differ between those who stopped and those who did not (Figure 2): Of the participants without antipsychotic medication throughout the study, 35.3% had a good outcome, and of those with antipsychotic medication 37.6% had a good outcome (Chi-Square Test = 0.097, df = 1, exact two-sided significance = 0.857). Neither did the more narrow definition: 18.6% of the participants with antipsychotic medication had at least one relapse compared to 23.5% of the "discontinuers" (Chi-Square Test = 0.665, df = 1, exact two-sided significance = 0.441). This inconsistency with the results of study 1 is resumed in the discussion.

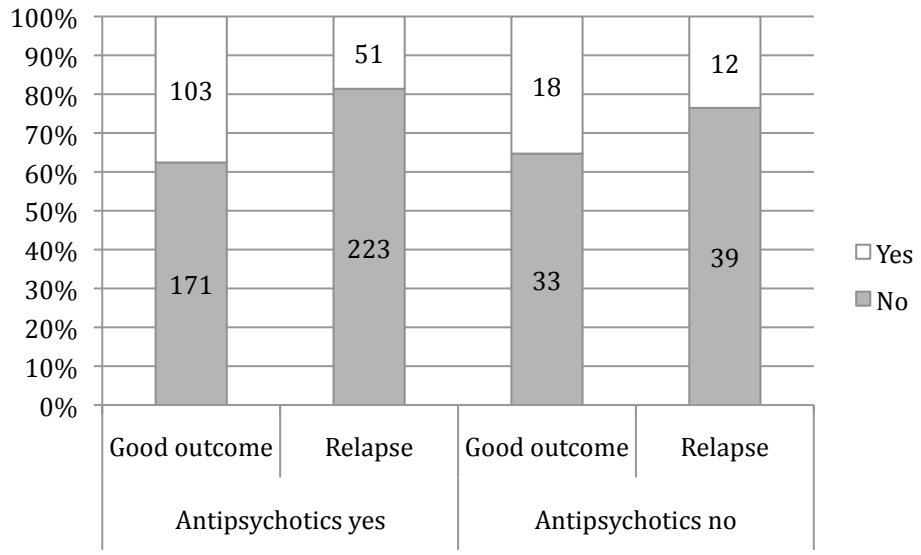

Figure 2: Illustrating that patients who stopped antipsychotic medication did not have a good outcome less often than those with antipsychotic medication.

Characteristics of successful "discontinuers"

Table 3a shows logistic regressions using "no relapse", the wider definition of a good outcome. The group of interest were successful discontinuers. They were compared to two reference groups: To the rest of the basic sample (Model A), and to patients with a relapse despite taking antipsychotics (Model B).

Table 3a: Logistic regression models for patients without relapse and who quitted antipsychotic medication (N=39): Model A: compared against the rest of the sample (N=281). Model B: compared against patients without antipsychotic medication but with relapse (N=12).

Model A*: "no relapse / no antipsychotics" (1) vs. "rest of the sample" (0)	B	SE	Wald	Df	P	Exp(B)	lCl	uCl
Region (1=WE/I, 0=EE/CE)	1.192	.370	10.360	1	.001	3.293	1.594	6.804
V1 ECG (1=normal, 0=abnormal)	-1.171	.452	6.716	1	.010	.310	.128	.752
V1 CDSS	.070	.034	4.088	1	.043	1.072	1.002	1.147
Model B**: "no relapse / no antipsychotics" (1) vs. "relapse / no antipsychotics" (0)	B	SE	Wald	Df	P	Exp(B)	lCl	uCl
Years of education	-.354	.164	.668	1	.031	.702	.509	.968

* 88.4% were classified correctly, R-Square: Cox and Snell=0.060, Nagelkerke=0.115. FSTEP entered: region, ECG, depression (CDSS).

** 76.5% were classified correctly, R-Square: Cox & Snell=0.115, Nagelkerke=0.173 (ENTER).

Comparing successful discontinuers against other patients, significant baseline predictors of no antipsychotics / no relapse were region (more common in Western and Central Europe), ECG, and depression (higher baseline scores) (Model A). Years of education separated the successful (fewer years of education) from the non-successful quitters in Model B.

Table 3b summarizes analyses analogous to table 3a, except that a more stringent definition of favourable outcome was used (no relapse and symptomatic remission).

Table 3b: Logistic regression models for patients with a good outcome and who quitted antipsychotic medication (N=18): Model A: compared against the rest of the sample (N=304). Model B: compared against patients without antipsychotics and without good outcome (N=33).

Model A*: "outcome+ / no antipsychotics" (1) vs. "rest of the sample" (0)	B	SE	Wald	Df	P	Exp(B)	lCl	uCl
Prognosis	-.535	.251	4.537	1	.033	.586	.358	.958
Social integration	.281	.119	5.612	1	.018	1.324	1.050	1.670
Model B**: "outcome+ / no antipsychotics" (1) vs. "outcome- / no antipsychotics" (0)	B	SE	Wald	Df	P	Exp(B)	lCl	uCl
Prognosis	-1.011	.360	7.887	1	.005	.364	.180	.737
Social Integration	.382	.180	4.521	1	.033	1.465	1.030	2.082

* 94.4% were classified correctly, R-Square: Cox and Snell=0.041, Nagelkerke=0.116. FSTEP entered: gender, prognosis (low = better), social integration, QOL. Gender was bivariately only near significance (p=0.051).

** 78.4% were classified correctly, R-Square: Cox & Snell=0.256, Nagelkerke=0.352. FSTEP entered: Age, gender, years of education, prognosis (low = better), social integration, CGI.

Using the narrower definition of favourable outcome, significant baseline predictors of no antipsychotics / no relapse were prognosis (better) and social integration (higher baseline scores with both reference groups (Models A, B).

Discussion

We examined a sample of patients suffering from first-episode schizophrenia who were all taking antipsychotic medication at study entry, with a focus on patients who discontinued medication. The large, international sample and the longitudinal study design used made it possible to study the characteristics of first episode patients who stopped taking antipsychotics and the consequences of discontinuation, on outcome. Most surprisingly, we were not able to detect a statistical difference in outcome between patients who discontinued medication and those who stayed on antipsychotics.

Patients living in West-European countries or Israel more often stopped taking any antipsychotic medication. Other variables significantly associated with stopping antipsychotic medication were: low compliance, better quality of life, and having a relapse (study 1). Neither psychotic symptoms, nor measures of severity of illness and functioning differentiated between patients who stopped and those who continued using antipsychotics.

Predictors of successful discontinuation varied with definition of success: Using a wider definition, the predictors of successful discontinuation were region (Western Europe/Israel) and ECG, paralleling the predictors of discontinuation in general, and a higher baseline level of depression. Successful discontinuers differed from unsuccessful ones just by fewer years of education. Using a more stringent definition of a good outcome which included remission next to not experiencing a relapse, better prognosis and better baseline social integration predicted successful discontinuation (study 2).

The decision process

The analyses confirmed the supposition that there were diverse decision-taking processes involved the decision to stop antipsychotic medication. The decision could be taken by patients alone, in accordance with their therapists, or be initiated by therapists. Two observations indicate that those decision rules were not primarily driven by criteria related to psychopathology:

- West-European or Israeli therapists and patients decided more often to continue without antipsychotic medication than their counterparts form Central- or East-European countries. This indicates that local clinical practice is involved in the decision.
- Patients and/or therapists in Central and East Europe seemed to be more likely to discontinue antipsychotics when patients' ECG was abnormal, probably because they feared cardiovascular problems.

This also illustrates that there is a range of actions regarding the decision whether to stop or to continue antipsychotic medication, which is exploited by some but not all therapists. This hypothesis is supported by the finding that - even if relapse was associated with stopping antipsychotic medication - at the 12-months-followup, patients who stopped did not have a worse outcome than those who continued. It will be of importance for future research to study practice guiding decisions about antipsychotic medication, considering the perspective that treatment without antipsychotics appears possible in the early phase of schizophrenia. Finally, evidence-based guidelines should be developed, indicating when it might be adequate to reduce or stop antipsychotic medication.

Stopping antipsychotic medication was associated with better subjective quality of life. This can be explained in various ways: Some patients may have experienced

remission and good quality of life, and therefore decided to stop medication because they felt they were not in need of it anymore. The close association of relapse to treatment discontinuation could also indicate the possibility of high quality of life being a result of low illness insight (quality of life was assessed by an interview and mirrors the subjective experiences of patients). Clearly, neither interpretation can be substantiated by this study. Interestingly, relapse was associated with stopping antipsychotic medication in study 1, but at the 12-month-followup the patients who had stopped antipsychotic medication did not relapse more often (study 2). In the Cox-regression used in study 1, relapse was entered as a time-variant predictor, which analyzes mean relapse status closest to the moment of antipsychotic discontinuation. This indicates that circumstances in temporal proximity to stopping medication around the moment of discontinuing need to be seen differently from those evaluated over a longer time span (in our case, the full one year observational period).

Successful discontinuation

Despite the small number of patients who stopped antipsychotic medication altogether, it was possible to identify predictors of successful discontinuation. But results have to be interpreted with caution due to low sample size. If patients with a very good outcome – operationalized as having had no relapse during the study and showing symptomatic remission at 12-months follow-up – were considered, prognosis of therapists and the baseline social integration of patients were quite good criteria for identifying patients who will do well without antipsychotic medication. Both variables have previously been identified as predictors of successful discontinuation by other groups: Bola et al. (32) reported that patients who discontinued medication had a better social functioning at baseline, and prognosis was determined as being

related to antipsychotic-free response in another study by the same group (33). Although the definition of outcome and the measures used by us differ from those two studies, the parallels regarding predictors are intriguing.

When a wider definition of successful discontinuation was used, namely having no clinical relapse during the study interval, the predictors of successful discontinuation were quite similar to the predictors of discontinuation (region and cardiac health), extended by higher baseline depression scores. The latter deserve some discussion: One cannot infer that first-episode patients with high initial depression scores are not as severely ill as patients with lower scores, as they did not have lower scores on the CGI. Neither were the differences in initial depression severity explained by diagnosis: The two diagnoses sometimes associated with better prognostic features, schizophreniform disorder and schizoaffective disorder, were not more common in the group of successful discontinuers. An earlier report from the same dataset describes higher initial depression scores to be associated with a better quality of life at follow up (34). High initial depression seems to be a positive prognostic factor, at least in the patient population studied in the EUFEST. This is in line with very early findings, which have suggested affective features to be a positive outcome predictor in schizophrenia (35) an issue which is still debated in the field.

Predictors of successful discontinuation differed with the outcome definition used. A favourable outcome in a more stringent definition, seemed to be easier to predict for therapists than the mere risk for relapse.

Implications

With all due condition two main implications can be entertained based on the results of this study: Firstly, it is an important task for future studies to identify the processes involved in the decision of therapists whether to encourage a patient to continue or

discontinue antipsychotic medication; this would help to develop more differentiated guidelines for clinicians and a better information base for patients. Secondly, depression, prognosis and social integration seem to be important candidates for predicting successful drug discontinuation; their exact role and interaction have to be examined in future studies.

Strengths and Weaknesses

The study was designed to mirror routine clinical practice in the participating centres. Therefore, it was possible to identify regional differences. Results of secondary analyses like ours, while helping to generate hypotheses which can be prospectively tested in future studies, clearly cannot serve as the basis for an evidence-based decision process regarding the feasibility of discontinuing antipsychotic treatment in first episode patients.

Another limitation pertains to the length of follow-up. One year is definitely not long enough to judge the outcome of first episode psychosis. Earlier studies with longer observation periods have shown an ongoing progressive relapse risk beyond one year. It is not unlikely that a number of the “successful discontinuers” in our study may have experienced a relapse later on. Therefore our findings could be overoptimistic with regard to relapse free antipsychotic discontinuation. On the other hand, we may have underestimated proportions of remitted patients in EUFEST. As a six-month duration of symptomatic remission is part of the stricter remission criteria (23), patients who for instance have reached the symptomatic criteria 9 months into the trial could have, by definition, never met full criteria in our one year study.

Lastly, as discussed in the primary paper (21), this was an open clinical trial with all the potential observation and reporting biases. Especially it could not be determined whether patients or therapists decided to discontinue or whether this was a joint

decision. On the other hand, the pragmatic study design reflecting every day clinical practice and the large overall sample size can be considered strengths of this clinical trial.

Conclusions

In a secondary analysis of the EUFEST, we have identified a significant number of patients who discontinued antipsychotic medication and had a good outcome nevertheless. Good premorbid social functioning, high depression scores at baseline and a clinician's subjective evaluation of prognosis were found to predict favorable outcome. Results of our study should help to design future studies in which patients, who may be able to successfully discontinue medication after a first episode of psychosis, can be prospectively identified. This would add to the evidence base of the long term clinical management of patients suffering from a first episode of schizophrenia.

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Curriculum Vitae

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Since 2005:	Research Assistant Public Mental Health, Psychiatric University Hospital Zurich, Prof. Dr. med. Dipl.-Psych. Wulf Rössler; Working in different projects, e.g. ZInEP, subproject Epidemiology; Zurich-Study, and other, smaller projects.
2002 – 2005:	Project leader Kompetenzzentrum Arbeit, City of Berne (Work reintegration)
1994 – 2001:	Master of Science in Clinical Psychology, University of Zurich, Zurich
1997 – 2000:	Work in a Home-Care institution for the elder (SPITEX), Zurich
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Appendix

I Study 1: Unmet needs in patients with first-episode schizophrenia: a longitudinal perspective

Published in: Psychological Medicine, 2012 Jul;42(7):1461-73.

doi: 10.1017/S0033291711002406. Epub 2011 Nov 21.

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Abstract

Background:

This study aimed to identify the course of unmet needs by patients with a first episode of schizophrenia and to determine associated variables.

Methods:

We investigated baseline assessments in the EUFEST trial as well as follow-up interviews at 6 and 12 months. Latent class growth analysis was used to identify patient groups based on individual differences in the development of unmet needs. Multinomial logistic regression determined the predictors of group membership.

Results:

Four classes were identified. Three differed in their baseline levels of unmet needs while the fourth had a marked decrease in such needs. Main predictors of class membership were prognosis and depression at baseline, and the quality of life and psychosocial intervention at follow-up. Depression at follow up did not vary among classes.

Conclusions:

We identified subtypes of patients with different courses of unmet needs. Prognosis of clinical improvement was a better predictor for the decline in unmet needs than was psychopathology. Needs concerning social relationships were particularly persistent in subtypes who remained high in their unmet needs and who lacked additional psychosocial treatment.

Introduction

Despite continuing efforts within the framework of early intervention programs to identify persons at risk, the initial contact with mental health services often coincides with a first episode of schizophrenia (Klosterkotter *et al.*, 2005, Lester *et al.*, 2009, McGorry *et al.*, 1996, Ruhrmann *et al.*, 2010). Early treatment reduces the potential for an unfavourable course that comprises persistent symptoms, (re-)hospitalisations, and deficits in social and vocational functioning (Addington *et al.*, 2007, Barnes *et al.*, 2008, de Koning *et al.*, 2009, Farooq *et al.*, 2009, McGorry *et al.*, 2010, Perkins *et al.*, 2005). First-episode patients benefit from a treatment approach that decreases psychopathological symptoms but also focuses on psychosocial functioning (Penn *et al.*, 2005). In many cases, such functioning has already deteriorated before the exacerbation of the first psychosis; in young people, psychosocial development is impaired by the illness and those persons remain at a low level of functioning (Hafner *et al.*, 1999). Most of the negative changes in social disability attributed to schizophrenia occur in the first two to five years of illness (an der Heiden and Hafner, 2000). Thus, stopping this process is a core component of successful treatment (an der Heiden and Hafner, 2000). One way to develop better treatment strategies is to monitor changes in treatment needs over time and to identify the conditions under which they arise.

Assessing treatment needs is an established element of clinical practice and service evaluation. In this context, needs are defined as the potential to benefit from (mental) health care (Wiersma, 2006), i.e., reversing a deficit via treatment. A more realistic definition states that needs are the prerequisite for maintaining or restoring an acceptable level of social independence and quality of life (McCrone *et al.*, 2001).

The concept of needs has been criticised because it pre-supposes an effective, but general, treatment that works for every patient with a given diagnosis, and for confounding the identification of a need with its potential solution (Priebe *et al.*, 1999a). Nevertheless, the widespread use of needs-assessment in research and practice calls for critical appraisal.

Several interviews for assessing needs for care have been developed. The most commonly applied are the Needs for Care Assessment (NCA) (Brewin *et al*., 1987) and the Camberwell Assessment of Need (CAN) (Phelan *et al.*, 1995), developed in the 1990s. The NCA includes an elaborate evaluation of psychopathology and psychosocial status. Because the NCA - and its revised form, the CNS (Marshall *et al.*, 1995) - is more extensive than the CAN, usually the latter is used in larger studies (Kilian *et al.*, 2001).

The CAN inquires about 22 potentially problematic areas of living, and differentiates among 1) ‘met needs’ (patient has a specific need and this need is met by treatment), 2) ‘unmet needs’ (specific needs that are not met by treatment), and 3) ‘no needs’ (patient does not have a need in this area of living). Several attempts have been made to establish groupings of the CAN items. Results from studies using data reduction techniques have been inconsistent (Korkeila *et al.*, 2005, Wennstrom *et al.*, 2004), and none of the factor solutions has become widely accepted or replicated. Here, we propose an alternative approach in which several classes of patients are identified who show different trajectories of needs over time.

Most research using the CAN considers only patients with a chronic or well-established illness. We believe that ours is the first study to adopt that approach in

determining needs within first-episode schizophrenia. Treatment of acute episodes can be divided into three phases. The acute phase (weeks or a few months) is followed by a post-acute stabilisation phase (3 to 6 months), and then by a stable phase of (partial) remission (months to years) (DGPPN, 2006). All of these phases should be examined when evaluating the progression of needs in first-episode patients over time.

Aims of the study

Three questions are addressed by the present study:

1) What is the course of needs over a 12-month period in first-episode patients compared with chronic schizophrenia patients?

2) Can we identify clusters of patients with different trajectories of unmet needs?

3) If so, what are the variables associated with those trajectories?

Methods

Database

Our study utilized data from the European First Episode Schizophrenia Trial (EUFEST) (Fleischhacker *et al*., 2005, Kahn *et al*., 2008). There, four second-generation antipsychotics (amisulpride, 200 to 800 mg; olanzapine, 5 to 20 mg; quetiapine, 200 to 750 mg; and ziprasidone, 40 to 160 mg) were compared against each other and against treatment with a low dose of haloperidol (1 to 4 mg) (Kahn *et al*., 2008). The main outcome measure was one-year medication retention rates, i.e., the proportion of patients who continued with the same medicament and the initial dosage. In addition, a battery of outcome and diagnostic measures was assessed at defined time points for all patients who did not withdraw informed consent or drop out for other reasons. The present study investigated a selection of those measures.

Sample

Fifty mental health centres in 13 European countries and Israel were selected for participation. Altogether, 1047 patients were screened for eligibility between December 2002 and January 2006. Inclusion criteria were ages 18 to 40 years; a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder; onset of positive symptoms dating back two years at most; use of antipsychotic drugs for at most two weeks in the previous year or for at most six weeks at any time; and no known intolerance or contraindication for one of the study drugs. Diagnoses were confirmed by the International Neuropsychiatric Interview (MINI plus) (Sheehan *et al.*, 1998). In all, 498 patients gave informed consent and were randomly assigned to five treatment groups. The study protocol was evaluated by local ethics committees or review boards according to country-specific laws.

Attrition rate

Attrition was not similar to loss of retention of the study drug, because patients were followed-up beyond loss of retention. Of the 498 patients initially included, 342 (68.7%) completed the assessments scheduled by the study according to protocol. Of the 156 withdrawals (31.3% of the baseline total sample), investigators withdrew six, while another four did not meet the inclusion criteria. The remaining 146 patients decided by themselves not to continue the study by withdrawal of consent or no-show. Figure 1 presents an adapted flow chart for the sample used in our analyses (blue boxes). More details about the entire trial are included within the main EUFEST paper (Kahn *et al.*, 2008).

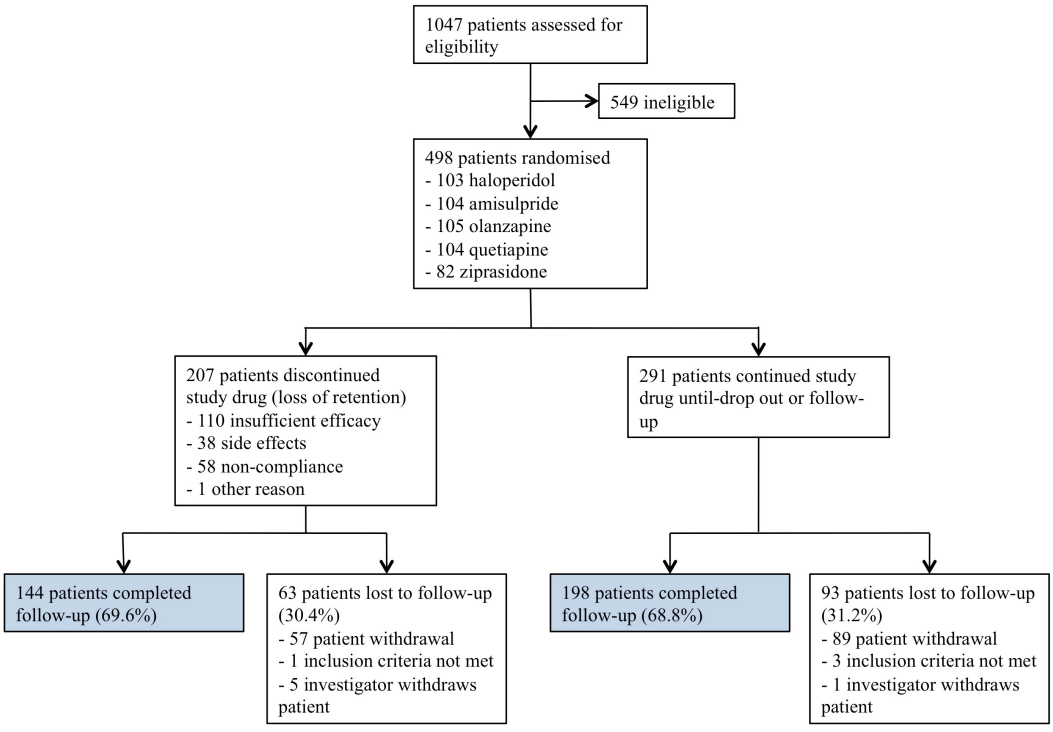

Figure 1: Simplified flow chart to illustrate the sample used here. Blue colouring indicates 342 patients who completed the study according to our protocol - but independently of the trial randomisation - and thus were included in the present analyses.

Measures

Met and unmet needs were evaluated per the Camberwell Assessment of Need (Phelan *et al.*, 1995). The CAN assesses ratings by patients as well as by therapists, caseworkers, or research assistants. Because scores can differ substantially between patients and professionals, it is important to consider whose perspective is reported when needs are discussed (Hansson *et al.*, 2001, Issakidis and Teesson, 1999, Lasalvia *et al.*, 2000, Macpherson *et al.*, 2003, Priebe *et al.*, 1999a, Slade *et al.*, 1998, Slade *et al.*, 1996, Wennstrom and Wiesel, 2006, Wiersma, 2006). Validity and reliability were previously established in several studies and deemed acceptable (Phelan *et al.*, 1995). In the original paper, inter-rater reliability was r=0.99 (patients) and r=0.98 (staff), test-retest reliability between r=0.78 (patients) and r=0.71 (staff) (Phelan *et al.*, 1995). However, test–retest reliability was not adequate for some single items (Kilian *et al.*, 2001), but this could be due to skewed distributions of the respective items (Phelan *et al.*, 1995).

We also used the PANSS (Positive And Negative Syndrome Scale) (Kay *et al.*, 1987), the MANSA (Manchester Short Assessment of Quality of Life) (Priebe *et al.*, 1999b), the CDSS (Calgary Depression Scale for Schizophrenia) (Addington *et al.*, 1993), and the GAF (Global Assessment of Functioning) (Jones *et al.*, 1995). In addition, the Hayward scale assessed compliance (a one-item seven-point rating scale, with higher scores suggesting better adherence) (Kemp *et al.*, 1998), while prognosis was evaluated along a six-point scale that ranged from 1 = best to 6 = bad.

The PANSS measures positive and negative symptoms and the general psychopathology of schizophrenia. Consisting of 30 items, it is scored by a trained

rater during a structured interview of 30 to 40 minutes. Leucht *et al.* (2005) have proposed that a percent reduction of 50% - respectively of 25% in treatment refractory patients - indicates treatment success. We use the 50% criteria even if the exact level of symptom reduction indicating response has been debated (e.g. Kinon *et al.*, 2008), because this was just used to describe the sample. The percent reduction was calculated after subtracting 30 (the minimal score) from the PANSS sum score. The CDSS is a nine-item scale that measures, with good reliability, the level of depression in schizophrenia (Addington *et al*., 1992). A cut-off of seven points refers to a specificity of 82% and a sensitivity of 85% for detecting major depressive episodes (Addington *et al.*, 1993).

The 14 participating countries were clustered into two regions: West European (The Netherlands, Belgium, France, Switzerland, Austria, Germany, Sweden, Spain, and Italy) and East and Central European (Bulgaria, Poland, Romania, and Czech Republic). Because only a few patients were from Israel, that country was added to the West-European category to control for cell sizes and confidence intervals in the analyses.

Socio-demographic variables were assessed at the beginning of the study (baseline, 0 months). At each assessment, relapse and psychosocial interventions were described. Episodes of psychosocial treatment were recorded with beginning and ending dates. Compliance with medication was measured at 1, 6, and 12 months. All other measures were assessed at least at baseline, 6, and 12 months[1]. Observer-rated measures were assessed by site coordinators or co-investigators, e.g., psychiatrists (including trainees), research nurses, or psychologists.

[1] CAN: 0, 6, 12 months; PANSS: 0, 1, 3, 6, 9, 12 months; MANSA: 0, 3, 12 months; CDSS: 0, 1, 3, 6, 12 months; GAF: 0, 1, 2, 3, 6, 9, 12 months; Hayward Compliance: 1, 6, 12 months.

Statistical analyses

The analyses are preceded by a comparison between the baseline sample characteristics of completers and the baseline characteristics of the complete sample. We used SPSS (PASW Statistics 18.0 for Windows) to calculate t-tests for continuous variables (or the non-parametric equivalent Mann-Whitney test for variables with non-normal distributions) and Chi-square statistics for categorical variables.

Because we were interested in individual trajectories of unmet needs over three time points, we developed a latent class growth model via Latent Gold 4.5. This modelling technique identifies different types of patients by estimating continuous latent variables for individual intercepts and slopes, as well as a categorical latent variable that represents groups with similar trajectories (Nagin, 1999). The analysis was based on the sum score of unmet needs. Our aim was to identify groups of patients as determined by maximally distinct trajectories of needs between groups and minimally distinct individual trajectories within groups. The number of groups was obtained statistically by comparing the model-fit indices of models with successive numbers of clusters. Because data were sparse, model significance (*P*-value associated) with the L^2 fit statistic was assessed using the bootstrap option within Latent Gold 4.5 rather than with standard chi-square values. Model fit was based upon the Bayesian Information Criterion (BIC). To decide on the final model, statistical fit indices were supplemented by the criteria of suitability for answering the research question, parsimony, theoretical justification, and interpretability (Muthén and Muthén, 2000). The sum of unmet needs was defined as a count variable.

Finally, we determined the predictors of membership for latent clusters of unmet-needs trajectories and the outcomes of clusters. Although Latent Gold 4.5 allows one to include predictors directly, that option is restricted to categorical variables. Because the measures used in this EUFEST study were count, ordered-categorical, or continuous, we preferred a multinomial logistic regression with cluster membership as the dependent variable. In the bivariate multinomial regressions, associated variables were selected on the basis of their significance (P<0.1 to consider weak effects also). Positive and negative symptoms, insight (one item from the PANSS), gender, region, and age were included by default. In the outcome model, follow-up values for the same longitudinal variables were used, and information was added for the number of relapses and psychosocial intervention (duration of one month or longer). In the combined multinomial regression model, variables with significant Likelihood Quotient Test (P<0.05) were considered main influences. Those that discerned only one group from another due to a significant odds ratio, but without any significant Likelihood Quotient Test, were also discussed. Multinomial regression was calculated with SPSS.

Differences in single needs that arose between assessment periods were not subjected to statistical testing because of limited cell sizes.

Results

Sample characteristics

The sample of study completers was used in our analyses. The mean age was 26.1 years at baseline, and more men (56.4%) participated than women (Table 1). Greater

than half of the sample (59.6%) was from Central and East European countries. Paranoid schizophrenia (45.3%) and schizophreniform disorder (40.1%) were the most prevalent diagnostic categories.

Table 1: Descriptive statistics of selected variables at baseline (total sample, N=498) and sample of completers (N=342).

	Baseline total		*Baseline completers*		*Dropouts*		*Difference: dropouts – completers*[2]
	mean ±SD / percent	*N*	*mean ±SD / percent*	*N*	*mean ±SD / percent*	*N*	*P*
Age at baseline (yr)	*25.98 ±5.55*	*(498)*	*26.05 ±5.64*	*(342)*	*25.83 ±5.38*	*(156)*	*0.618*
Gender (women)	*40.2%*	*(200)*	*43.6%*	*(149)*	*32.7%*	*(51)*	*0.024*
Cultural region							*0.000*
West Europe	*34.9%*	*(174)*	*28.9%*	*(99)*	*48.1%*	*(75)*	*-*
East/Central Europe	*51.4%*	*(256)*	*59.6%*	*(204)*	*33.3%*	*(52)*	*-*
Israel	*13.7%*	*(68)*	*11.4%*	*(39)*	*18.6%*	*(29)*	*-*
Occupation at baseline (yes)	*46.6%*	*(231)*	*46.5%*	*(159)*	*46.8%*	*(72)*	*1.000*
Antipsychotic naïve at baseline	*32.5%*	*(162)*	*30.7%*	*(105)*	*36.5%*	*(57)*	*0.216*
DSM-III-R diagnosis							*0.603*
Disorganized, catatonic, undifferentiated	*8.4%*	*(42)*	*7.3%*	*(25)*	*10.9%*	*(17)*	*-*
Paranoid	*44.8%*	*(223)*	*45.3%*	*(155)*	*43.6%*	*(68)*	*-*
Schizophreniform	*39.8%*	*(198)*	*40.1%*	*(137)*	*39.1%*	*(61)*	*-*
Schizoaffective	*7.0%*	*(35)*	*7.3%*	*(25)*	*6.4%*	*(10)*	*-*
Met needs patient, sum	*2.59 ±2.57*	*(470)*	*2.78 ±2.73*	*(333)*	*2.15 ±2.06*	*(137)*	*0.007/0.034*
Unmet needs patient, sum	*2.04 ±2.07*	*(470)*	*2.19 ±2.14*	*(333)*	*1.66 ±1.82*	*(137)*	*0.012/0.013*
MANSA	*4.04 ±0.92*	*(483)*	*3.98 ±0.90*	*(339)*	*4.19 ±0.96*	*(144)*	*0.023/0.022*
GAF	*40.03 ±13.51*	*(490)*	*40.72 ±13.50*	*(341)*	*38.46 ±13.44*	*(149)*	*0.087/0.107*
PANSS total score	*88.53 ±20.63*	*(487)*	*89.06 ±20.69*	*(340)*	*87.29 ±20.49*	*(147)*	*0.386/0.371*
PANSS positive symptoms	*23.13 ±6.19*	*(489)*	*23.36 ±6.17*	*(340)*	*22.59 ±6.23*	*(149)*	*0.205/0.138*
PANSS negative symptoms	*21.23 ±7.62*	*(489)*	*21.14 ±7.73*	*(341)*	*21.42 ±7.41*	*(148)*	*0.714/0.793*
CDSS, sum score	*5.07 ±4.87*	*(488)*	*5.27 ±4.88*	*(341)*	*4.62 ±4.84*	*(147)*	*0.176/0.140*
Prognosis by investigators	*3.19 ±1.19*	*(495)*	*3.10 ±1.18*	*(342)*	*3.39 ±1.19*	*(153)*	*0.014/0.014*
Compliance (at 1 month)	*5.57 ±1.20*	*(453)*	*5.66 ±1.16*	*(337)*	*5.30 ±1.29*	*(116)*	*0.006/0.006*

Significant, but not large dropout effects (differences in baseline scores between completers and dropouts) were found for the following variables: gender (more male dropouts), region (fewer dropouts in East- and Central European countries), treatment compliance (more adherent patients completed the study), and prognosis

[2] Significance of differences between baseline completers and dropouts was calculated for each continuous/count/ordinal variable with t-tests (first *P*-value), to control for non-normal distributions with the Mann-Whitney Test (second *P*-value), and with chi-square tests for nominal variables.

(completers had a better prognosis). Finally, completers had more met and unmet needs at baseline than did dropouts.

From baseline to 12 months of follow-up, 78.7% (263 of 334 completers) reached a 50% reduction in their PANSS total scores. At baseline, 36.1% (123 of 341) had a diagnosis of major depression according to the CDSS score; at 12 months, this was only 3.5% (12 of 340). Most subjects were part of inpatient treatment settings at the beginning of the study (89.8%; 307 of 342) versus only 4.7% (16 of 340) at the 12-month follow-up. About 32.5% of the patients (111 of 342) had received some psychosocial treatment during at least one month.

Figure 2 depicts the course of patient-rated met and unmet needs, measured by the CAN. Both clearly decreased from baseline to six months. While the number of met needs continued to decline in the second half of the study, the amount of unmet needs tended to remain stable over that period. Compared with baseline findings, at 12 months 65.0% (N=208) patients had fewer unmet needs, 27.5% had an equal number, and 7.5% (24) had more. At baseline, met needs were slightly more frequent than unmet needs (ratio met/unmet = 1.41), but after 6 and 12 months, at least two out of three needs were met (ratio met/unmet = 2.41 and 1.96, respectively) (Figure 2).

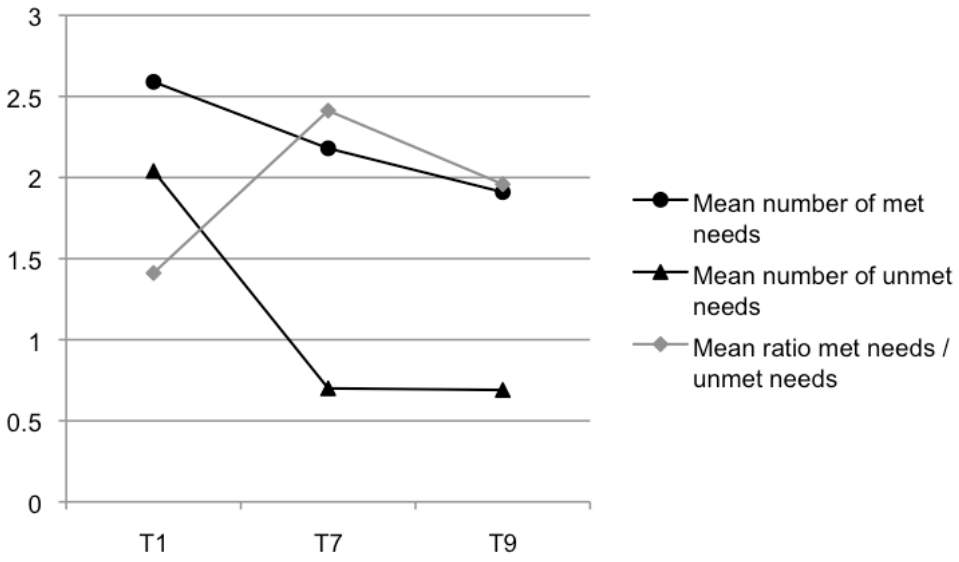

Figure 2: Means for number of met needs, unmet needs, and ratios for met needs / unmet needs according to patient ratings from baseline (T1) to 6 months (T7) and 12 months (T9) in the EUFEST trial. All patients providing CAN ratings at the respective assessments were included.[3]

Differences in the course of unmet needs between patient classes

A four-class model describing the course of unmet needs best fitted the data (Figure 3). This solution fulfilled other criteria of model usability, being practical and easy to explain (Muthén and Muthén, 2000). Class 1 (autonomous group) had few unmet needs and a diminishing trend between baseline and six months. A second started with a mean of 2.5 unmet needs, then declined sharply to 1.25 from baseline to six months and slowly to 1.15 afterward (ordinary group, Class 2). Our uncomplicated group (Class 3) started with 4.5 unmet needs, then markedly decreased to nearly zero unmet needs in the first six months before showing no other change. Finally, Class 4 (complicated group) began with nearly 5.0 unmet needs at baseline, which

[3] Ratios: If a person indicated no unmet needs, the respective case was set to the „system missing" value. Therefore, the sample from ratios is much smaller than the sample used for sum scores.

distinctly dropped to 3.75 at six months before increasing to 4.0 unmet needs by Month 12.

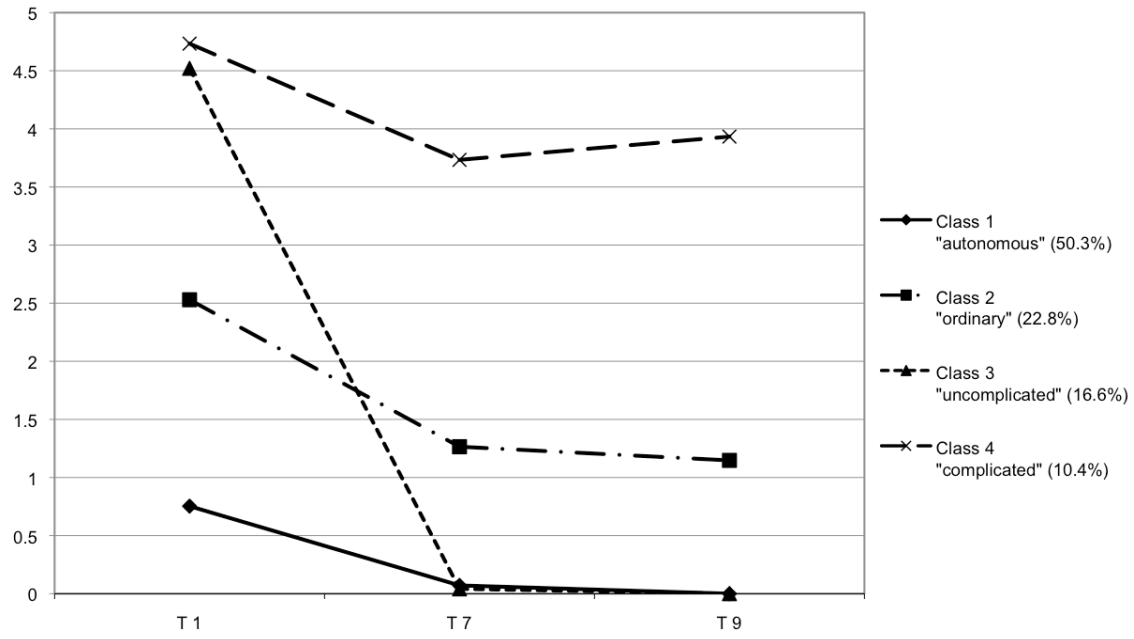

Figure 3: Four-class model of sum of unmet-need patient ratings (Total N=338). Lines represent mean number of unmet needs in each class.[4] T1=Baseline, T7=6 months, T9=12 months.

When the ratio of met to unmet needs was considered, change in the first six months was greatest in the uncomplicated group, i.e., from a ratio of 0.74 at baseline the ratio increased to 4 met needs per 1 unmet need (N=2). In contrast, ratios for the complicated class remained relatively stable over the three time points (0.80, 1.51, 1.37).

[4] The four-class model was selected according to the BIC criterion. Class sizes were N(c1)=170, N(c2)=77, N(c3)=56, N(c4)=35.

Predictors and outcomes of needs course

Covariates of the course of unmet needs that were significant at $P<0.1$ in bivariate analysis were combined in one multinomial regression model. Positive and negative symptoms as well as the item "insight" from the PANSS were included by default. Table 2 shows our results from the multinomial regression analysis of baseline variables. The autonomous group was chosen as the reference class. From our model, the significant predictors at baseline were depression (means: Class 1 = 4.17, Class 2 = 5.25, Class 3 = 8.00, Class 4 = 6.51), prognosis (Class 1 = 2.92, Class 2 = 3.43, Class 3 = 2.93, Class 4 = 3.60), age (Class 1 = 25.78, Class 2 = 27.26, Class 3 = 25.06, Class 4 = 26.16), region (West Europe and Israel, Class 1 = 33.5%, Class 2 = 53.2%, Class 3 = 41.1%, Class 4 = 37.1%) and being antipsychotic naïve (Class 1 = 32.9%, Class 2 = 26.0%, Class 3 = 39.3%, Class 4 = 14.3%) according to the Likelihood Quotient Test ($P>0.05$). Patients in the ordinary group had less favourable prognoses than those in the reference group. Persons with an uncomplicated course were distinguished from the autonomous group only by higher depression scores and lower quality of life at baseline. Patients with a complicated-needs course were more often male, had higher baseline depression scores, a less favourable prognosis, and lower compliance. Moreover, they included more patients who already had used antipsychotic medication before the study began. Prognosis at baseline indirectly separated the complicated from the uncomplicated group.

Values for variables used in the baseline model – age, region, and gender – were included in the follow-up model (Table 2), as were the number of relapses and psychosocial intervention (duration of at least one month). Psychosocial interventions (Class 1 = 35.3%, Class 2 = 42.9%, Class 3 = 25.0%, Class 4 = 11.4%) and quality of life (Class 1 = 5.06, Class 2 = 4.66, Class 3 = 4.82, Class 4 = 4.16) were

significant covariates in the model (Likelihood Quotient Test $P>0.05$). None of the follow-up variables differentiated between the autonomous (reference) and the ordinary group. The uncomplicated group had lower functioning scores at follow-up compared with the reference group. The complicated group had fewer psychosocial interventions, lower quality of life, more positive symptoms, fewer negative symptoms, and better compliance than did the autonomous group (Table 2).

Table 2: Baseline and follow-up covariates of unmet needs by different trajectory classes (total N = 331 at baseline and N = 327 at follow-up). Reference class: Class 1 "autonomous" (N=167).[5] [6]

	Class 2 "ordinary"		**Class 3 "uncomplicated"**		**Class 4 "complicated"**	
	OR	*(lower-upper 95% CI)*	*OR*	*(lower-upper 95% CI)*	*OR*	*(lower-upper 95% CI)*
Baseline						
GAF functioning	*0.99*	*(0.97-1.01)*	*0.98*	*(0.95-1.00)*	*0.97*	*(0.93-1.01)*
CDSS Depression score	*1.04*	*(0.97-1.11)*	***1.14***	***(1.06-1.23)***	***1.13***	***(1.02-1.25)***
MANSA Quality of Life	*0.70*	*(0.49-1.01)*	***0.63***	***(0.41-0.97)***	*0.60*	*(0.36-1.02)*
PANSS positive	*1.00*	*(0.94-1.06)*	*1.04*	*(0.97-1.11)*	*0.95*	*(0.86-1.04)*
PANSS negative	*0.99*	*(0.95-1.03)*	*0.96*	*(0.92-1.01)*	*0.95*	*(0.89-1.01)*
PANSS insight	*1.02*	*(0.80-1.31)*	*0.86*	*(0.64-1.15)*	*0.81*	*(0.55-1.18)*
Prognosis[a]	***1.33***	***(1.03-1.73)***	*1.07*	*(0.78-1.47)*	***1.74***	***(1.16-2.60)***
Compliance 1 month	*0.92*	*(0.69-1.22)*	*0.99*	*(0.70-1.39)*	***0.62***	***(0.42-0.92)***
Age	*1.05*	*(1.00-1.10)*	*0.96*	*(0.90-1.03)*	*0.99*	*(0.91-1.07)*
Men (ref)[b]	*.*		*.*		*.*	
Women	*0.55*	*(0.30-0.95)*	*0.69*	*(0.35-1.38)*	***0.35***	***(0.14-0.89)***
East/Central Europe (ref)	*.*		*.*		*.*	
West Europe	*1.85*	*(0.98-3.48)*	*1.12*	*(0.54-2.33)*	*0.37*	*(0.13-1.09)*
Occupation yes (ref)	*.*		*.*		*.*	
Occupation no	*1.41*	*(0.76-2.63)*	*1.07*	*(0.53-2.16)*	*2.37*	*(0.86-6.55)*
Not naïve (ref)	*.*		*.*		*.*	
naïve	*0.60*	*(0.31-1.16)*	*1.09*	*(0.54-2.21)*	***0.20***	***(0.06-0.68)***
Follow-up						
GAF functioning	*0.98*	*(0.95-1.01)*	***0.97***	***(0.93-1.00)***	*0.96*	*(0.92-1.00)*
CDSS Depression score	*1.03*	*(0.88-1.20)*	*0.97*	*(0.80-1.17)*	*1.15*	*(0.94-1.41)*
MANSA Quality of Life	*0.67*	*(0.42-1.07)*	*0.68*	*(0.40-1.13)*	***0.30***	***(0.15-0.60)***
PANSS positive sym.	*1.10*	*(0.99-1.22)*	*1.09*	*(0.97-1.23)*	***1.15***	***(1.01-1.31)***
PANSS negative	*0.95*	*(0.89-1.02)*	*0.93*	*(0.87-1.01)*	***0.89***	***(0.80-0.98)***
PANSS insight	*1.02*	*(0.73-1.41)*	*0.76*	*(0.51-1.13)*	*0.91*	*(0.56-1.49)*
Compliance	*1.22*	*(0.97-1.53)*	*1.11*	*(0.86-1.42)*	***1.49***	***(1.05-2.13)***
Psych. interv. yes (ref)						
no	*1.05*	*(0.53-2.31)*	*1.98*	*(0.89-4.42)*	***5.82***	***(1.51-22.50)***
Number relapses	*1.34*	*(0.72-2.49)*	*0.98*	*(0.46-2.09)*	*1.31*	*(0.58-2.98)*
Age	*1.04*	*(0.99-1.10)*	*0.97*	*(0.91-1.04)*	*0.98*	*(0.90-1.06)*
*Men (ref)**	*.*		*.*		*.*	
Women	*0.60*	*(0.32-1.12)*	*0.84*	*(0.43-1.65)*	***0.38***	***(0.14-1.00)***
East/Central Europe (ref)	*.*		*.*		*.*	
West Europe	*1.84*	*(0.53-2.06)*	*1.39*	*(0.62-3.07)*	*1.02*	*(0.33-3.09)*

[a] *Prognosis is inversely scored: higher scores mean a more unfavourable prognosis*

[b] *Reference Category. This parameter is set to zero because it is redundant.*

Specific unmet needs

In all four classes, daytime activities, psychotic symptoms, psychological distress, and social integration were most often rated as unmet needs (Figure 4a). In areas of life where unmet needs were prevalent at baseline, some still remained unmet after

[5] According to the Likelihood Quotient Test, the omitting of region, CDSS, being antipsychotic naïve at baseline, and prognosis led to significantly different models (P<0.05). Overall model fit: Chi-square 118.066, Df 39, P<0.000. Pseudo R-square: Cox & Snell 0.300, Nagelkerke 0.329, McFaden 0.148.

[6] According to the Likelihood Quotient Test, only the omissions of MANSA and psychosocial intervention led to significantly different models. Overall model fit: Chi-square 104.402, Df 36, P<0.000. Pseudo R-square: Cox & Snell 0.273, Nagelkerke 0.300, McFaden 0.131.

12 months. Met needs (Figure 4a) were more persistent, being associated with hardly any reduction in psychotic symptoms and social integration. Figure 4b depicts the change in specific unmet needs for each class. A bar corresponds to the total change in a particular item in the total sample (=100%). Each bar contains information on change in the four classes. The negative section of the bars represents fewer unmet needs at 12 months than at baseline while the positive portion corresponds to an augmentation in unmet needs. For example “intimate relationship”: change in class 1 = -6, change in class 2 = -1, change in class 3 = -18, change in class 4 = +7; total change in unmet needs = 28 (100%).

Those needs concerning self-care, sexual expression, education, and transport became more frequent in the ordinary group whereas those related to sexual expression, intimate relationship, company, education, looking after home, and money became more frequent in the complicated group.

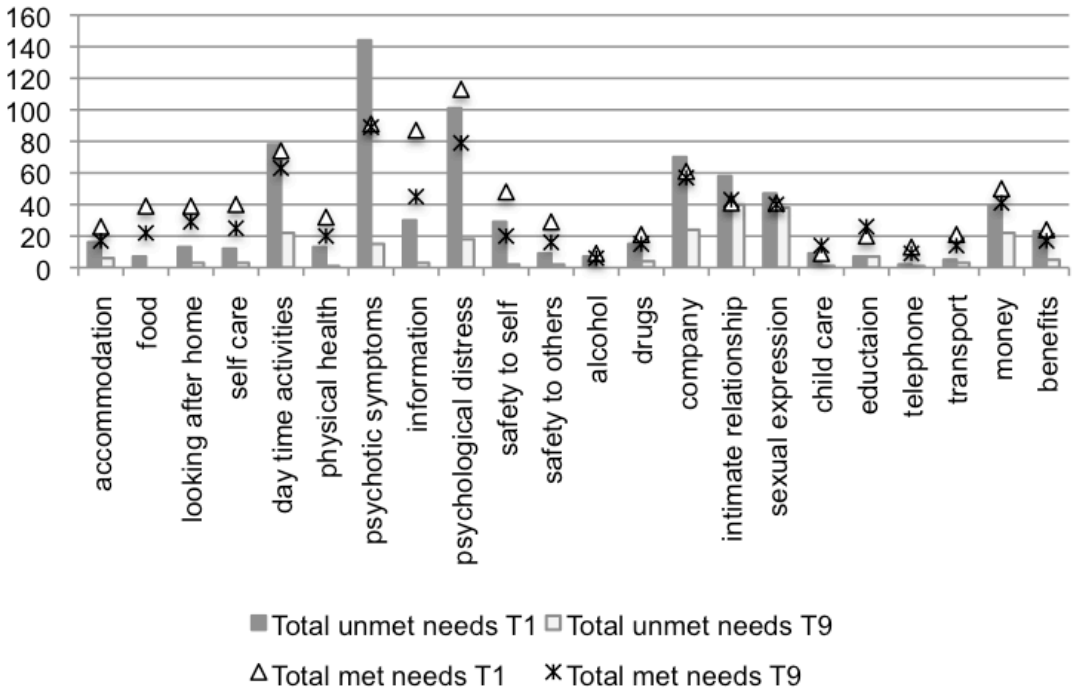

Figure 4a: Distribution of needs in detail. Bars represent numbers of met (triangles) and unmet (darker bars) needs at baseline (T1); crosses (met needs) and lighter bars (unmet needs) represent numbers of needs at the 12-month follow-up (T9).

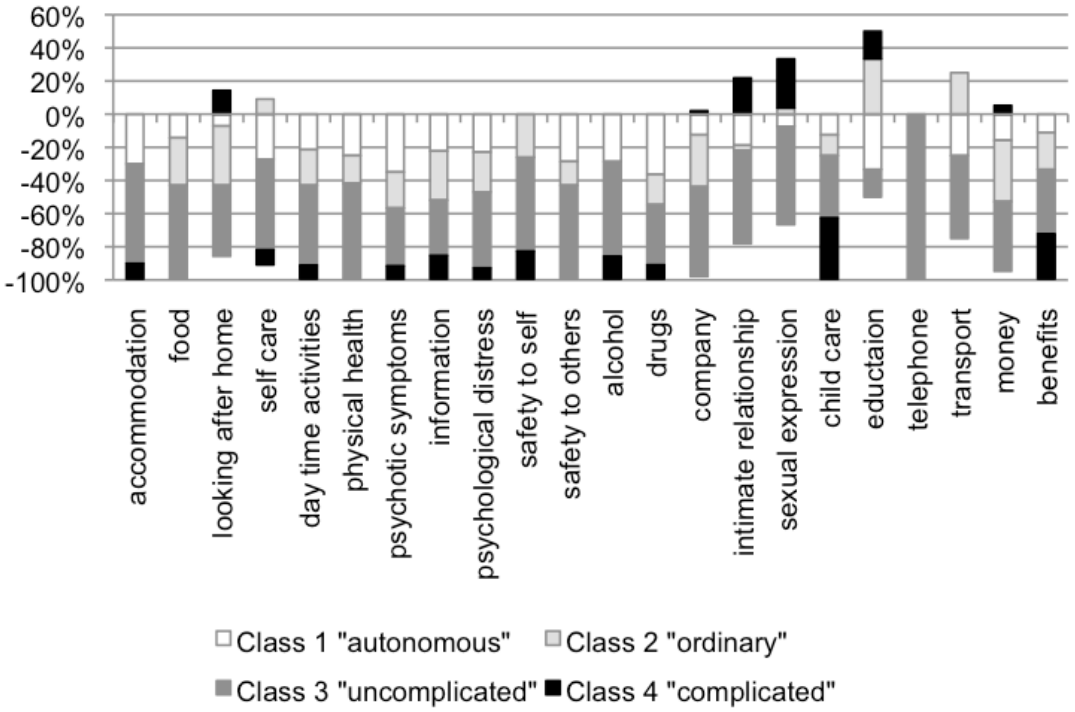

Figure 4b: Percent change between baseline (T1) and 12-month follow-up (T9) in single unmet needs in the four classes. 100% represents the total change in a particular item in the total sample. The coloured bars represent how much of this change was present in each of the latent classes. Positive values = more unmet needs, negative values = reduction in unmet needs.

Discussion

Information is scarce about the course of treatment needs for persons in the early stages of schizophrenia. We analyzed patient ratings of needs over a 12-month span in a homogenous sample of participants suffering from first-episode schizophrenia. It became clear that the first six months were of outmost importance to treatment because the largest proportion of change in needs occurred during that period.

The EUFEST sample contains many relatively well-integrated patients who possibly will never become chronically ill. Accordingly, the degree of reduction in unmet needs over time has proven more pronounced in that study than in other research encompassing the same time span in longer established illness (Priebe *et al.*, 2002). Because the EUFEST sample was homogenous for the phase of illness at baseline, the majority of patients made a transition from the acute phase of illness to remission after about six months. They then reached the stabilisation phase during the second half of the study. At least at baseline, all were under neuroleptic medication, which helped reduce symptoms and contributed to an initial decline in unmet treatment needs in the majority of patients. Neither the duration of medication nor first- versus second-generation neuroleptic medication had a significant impact on the course of unmet needs. However, a floor effect may have been responsible for the relatively stable course of unmet needs between 6 and 12 months.

The overall curve of unmet needs was composed of three groups that differed mainly in their baseline numbers of unmet needs, plus one relatively small group that showed a marked decline in those needs. The largest group had few unmet needs throughout the study. From the beginning, patients from this group had better

prognoses than those who remained higher in unmet needs. They also experienced less depression and a better quality of life than did patient groups with more initial unmet needs. This group was called the “autonomous” group because they had fewer unmet needs, even if they did not have more psychosocial interventions. The “ordinary” group had slightly more unmet needs throughout the study compared with the autonomous group, as well as a less favourable initial prognosis. Accordingly, more patients in this group underwent some type of psychosocial treatment. Although many of their unmet needs had disappeared by Month 6, those that concerned education and transport, which might become more important in more stable phases of illness, had increased. Patients in the “uncomplicated group” had relatively numerous unmet needs at the beginning but then showed a very steep decline from baseline until the six-month assessment, even if they did not have more frequent psychosocial treatment than the other two groups. Strong initial depression and low quality of life might have been reasons for the elevated number of unmet needs at baseline. Patients in the “complicated group” who had rather elevated levels of unmet needs over the entire time span had more initial depression, as was also found with the uncomplicated group. However, they seemed to miss the opportunity for recovery, as evidenced by their greater number of positive symptoms at follow-up compared with other groups. The lack of psychosocial interventions might have been a reason for this because patients’ psychosocial needs had increased at the time of follow-up.

Some processes that influence the course of unmet needs merit a closer look. For example, high depression scores at the beginning of our study coincided with a high degree of unmet needs. However, depression did not differ between the uncomplicated group with declining unmet needs and the complicated group that

sustained a high level of such unmet needs. Because depression during the follow-up period was no longer associated with various courses of needs, this finding cannot be explained by a self-rating bias of both instruments (Hansson *et al.*, 2007). Findings that concern predictions of later depressive episodes based upon depression in the prodromal or acute states are unequivocal (an der Heiden and Hafner, 2000, Birchwood *et al.*, 2000, Upthegrove *et al.*, 2010). Our results might also be interpreted as evidence that depression in the acute phases does not have to be exactly the same as depression in later phases of schizophrenia. Patients in acute phases of schizophrenia probably do not entirely realize that they need help because of their contemporaneous delusions and grandiosity. By contrast, depression implicates a stronger urge to seek assistance and greater insight into their illness, thereby leading them to a greater recognition of those needs (Mintz *et al.*, 2003, Schennach-Wolff *et al.*, 2011). By the later phases, working alliances might develop and patients may learn to rate their need for treatment independently of depressive symptoms. However, the missing impact of insight revealed in our study discounts this hypothesis.

Surprisingly, neither baseline positive nor negative symptoms were relevant. However, at follow-up, positive and negative symptoms as well as functioning differed among the groups. One possible conclusion is that neither psychotic symptoms nor depression and functioning in acute phases could predict whether patients would require more intensive help, especially with social needs. Nevertheless, at follow up there may have been larger differences among patients (i.e. whether they are in acute or stabilisation phase of illness), and therefore, stronger effects of psychopathology. A more profound examination of the topic would be interesting. For now, this lies beyond the scope of our paper.

The prognosis of clinical improvement appeared to discern the uncomplicated and complicated needs course in patients with initially high numbers of unmet needs. Thus, the prognosis was quite exact because patients remaining high in unmet needs also had more positive symptoms or lower functioning scores at follow-up. However, our data did not clearly indicate the basis upon which investigators drew their conclusions concerning prognosis. There, an ad-hoc scale was applied, for which psychometric properties have not been ascertained. Despite the correct prognosis at baseline, patients with a complicated needs course had less frequent psychosocial interventions. This could not have been explained as a failure to recognize their own needs because, at both baseline and follow-up, those patients had indeed expressed psychosocial needs. In general, the persistently high occurrence of unmet social needs in patients with a complicated course demonstrates the necessity to address social and relationship needs during both acute and post-acute phases of illness. Impairments in (social) functioning can also be very stable in the middle and late courses of schizophrenia (Hafner *et al.*, 1999). Antipsychotic treatment alone is not sufficient to improve such functioning (Swartz *et al.*, 2007). By attending to unmet social needs at the early stages, one can prevent the progressive loss of meaningful relationships. Although we could not obtain information for why those patients with many needs did not receive help, these results indicate the importance of studying the processes that lead to a clinical prognosis as well as the relationship between that prognosis and treatment-planning in first-episode patients.

Whereas revealing more unmet needs at follow-up coincided with better compliance, at baseline the opposite was true. Using univariate analysis, we found similar effects of compliance at baseline and follow-up. Therefore, compliance was better in patients

with more unmet needs later on, but only with regard to other variables that were included in the follow-up model.

Summary

Results from this study demonstrated that, in a sample of first-episode patients, strong differences were found among their one-year courses of treatment needs. An unfavourable course of unmet needs coincided with more positive symptoms. Psychosocial treatment seemed to play a critical role in influencing the development of unmet needs. Whether investigators are able to predict those courses and whether psychosocial treatment really is responsible for an improved needs course must be confirmed by studies that utilize more elaborate assessments. This may potentially identify those patients at risk for more unfavourable courses, thereby prompting attention to reduce their unmet needs.

Limitations

One limitation to the generalizing of these results was participants' attrition. Our results were valid only for patients who completed the study; it is unclear whether the data would have been the same if all patients had been included. We did not use imputation of missing values because they were not randomly distributed. Because unmet needs and several other variables were predictors of missingness, such imputation would have borne a high risk of biasing the results.

A second limitation lay within the analytic strategy. Low levels of unmet needs can be due to generally few needs, but may also be a consequence of many needs being met. The approach we used did not differentiate between those conditions.

Other limitations were due to instruments and study design. For example, the CAN is not devised especially for first-episode schizophrenia. If needs exist that are exclusively relevant in this phase of illness, they may be missed by the CAN. Needs were assessed during a controlled randomized trial that was aimed, instead, at testing different neuroleptic medications. Other factors may have influenced the course of unmet needs that were not addressed in this study.

Acknowledgments

This work was done without funding. The EUFEST trial was supported by the European Group for Research in Schizophrenia (EGRIS) with grants from AstraZeneca, Pfizer, and Sanofi-Aventis.

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II Study 2: The interrelation of needs and quality of life in first-episode schizophrenia

Published in: European Archives of Psychiatry and Clinical Neurosciences. 2012 Apr;262(3):207-16.

doi: 10.1007/s00406-011-0275-6. Epub 2011 Nov 24.

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Abstract

Background:

The interrelation between needs for care and quality of life has been described and replicated by several studies. The present work aims to add to the understanding of longitudinal interrelations between needs for care, quality of life, and other outcome measures by analyzing a sample of patients at the onset of schizophrenia.

Methods:

This study relied on data from the EUFEST trial, designed to compare first- and second-generation antipsychotics during one year. At baseline, 498 patients have been included. The first (baseline) and the last assessment (12 months after baseline) were used for the analyses. Predictors of quality of life were determined using regression analyses. We tested the complex longitudinal interrelations between baseline and outcome measures with structural equation models.

Results:

Unmet needs were not definitively confirmed as a predictor of subsequent quality of life, unless unmet needs changing to no needs were separated from unmet needs changing to met needs. Each unmet need that changed to no need enhanced quality of life (mean score 1 - 7) by 0.136 scale points.

Conclusions:

This study suggests that when studying quality of life and needs for treatment, it is crucial to differentiate whether unmet needs disappeared or whether they were met, as the former has a stronger impact on quality of life.

Introduction

Addressing the needs of psychiatric patients has become an important indicator for assessing the quality of mental health services. It is understood that each patient has individual needs but that there are illness specific needs common to patient groups. Needs of patients could, in principle, be satisfied by providing effective treatment. Needs are commonly differentiated into met and unmet. Unmet needs are ongoing serious problems of an individual patient, whether or not help is provided whereas met needs are absent or moderate problems because help is provided and successful [23]. For example an unmet need is when someone does not know where to live after leaving the hospital. The need is met when this person has an interim solution and receives help with finding a new apartment. Met needs are further distinguished from no needs, as they continue to be needs despite the temporary relief afforded by treatment. For example, no need is when the living situation of a patient is satisfactory. If previously unmet needs can be satisfied, or if the number of unmet needs has simply declined over time, it is assumed that treatment has been effective [31]. Although the assessment of treatment needs is widely used, its validity as an outcome measure remains contested as oversimplifying the process of clinical decision making and individual recovery processes of patients [24].

It is assumed that a change from unmet to met needs of patients should improve their quality of life [31]. Enhancing quality of life is a major goal of treatment, especially in patients suffering from severe and chronic mental disorders. Quality of life encompasses, as a broad outcome measure, satisfaction with several domains of individual life. The domains of quality of life and the domains of needs overlap in part

(e.g. living situation, work and social relations) [26]. At least a weak interrelation of the two concepts can be anticipated.

Usually, needs are assessed with structured interviews, the most common being the Camberwell Assessment of Need (CAN) [23], and the Needs for Care Assessment (NCA) [5]. Cross sectional studies [3, 9, 10, 32, 35, 39] have confirmed the interrelation between unmet needs and quality of life including patients with high, medium and low levels of functioning [3]. For met needs, the interrelation with quality of life was less consistent. Some studies found a negative association (the more met needs the lower the quality of life) [32, 39], others did not find such an association [10]. The assumption that more met needs would be associated with higher quality of life was not confirmed.

However, cross-sectional studies are not sufficient to resolve questions of causal interrelations. Longitudinal association is one criteria of establishing causality [4]. The few longitudinal studies testing the interrelation of quality of life and needs yielded inconsistent results. Slade and colleagues found that the average level of unmet needs and changes in unmet needs preceded quality of life [30]. Patient-rated unmet needs were a stronger predictor of subsequent quality of life than social role functioning, psychopathology, satisfaction with services, and therapists' ratings of needs [31]. Hansson & Björkman [9], on the contrary, did not find any longitudinal associations between needs and quality of life.

The aim of the present study was to gain greater insight in the longitudinal interrelation between quality of life, unmet needs, symptom severity, clinical status and social functioning. As a met need is defined as a need that is met by treatment, it

has to be differentiated from a need that has disappeared during treatment. Therefore we were interested whether the change from unmet needs to met needs [31], but also to no needs is associated with improvement in quality of life. The secondary aim was to describe the interrelation of needs and quality of life in a homogenous sample of patients moving from the acute first episode to the remission and stabilisation phases of schizophrenia.

Methods

Database

The present study used the data of the European First Episode Schizophrenia Trial (EUFEST) [8, 15]. The EUFEST study aimed to compare second-generation antipsychotics with low doses of haloperidol [15]. The main outcome measure was one-year retention rates of medication. In addition, a battery of outcome- and diagnostic measures was assessed at several defined points in time. The present study includes psychosocial and psychopathological outcome measures assessed at baseline and after 12 months, as needs and quality of life were assessed simultaneously only twice, at the beginning and end of the study. Although the EUFEST trial addressed some weaknesses of previous antipsychotic drug trials (for critique of previous studies see [19]), other methodological aspects can be criticised: Among other, EUFEST was not blinded [8] and thus is supposed to favour all second-generation antipsychotics [19]; also the analytic strategy used in EUFEST has been criticised [7]. But most critiques are focused on the comparison of first- and second-generation antipsychotics. The present study does not analyze medication, therefore most of this limitations do not apply. Limitations relevant to this study are discussed in the limitations section.

Sample

Fifty centres from 13 European countries and Israel were selected for participation. Altogether, 1047 patients were screened for eligibility between the December 2002 and January 2006. Inclusion criteria were age between 18 and 40 years, and a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder, onset of positive symptoms dating back at most two years; use of antipsychotic drugs

for at most two weeks in the previous year or for at most 6 weeks at any time; and no known intolerance or contraindication for one of the study drugs. Diagnoses were confirmed by the International Neuropsychiatric Interview (MINI plus [29]). 498 patients gave informed consent and were randomly allocated to five treatment groups. The study protocol was subjected to the local ethic committees or review boards according to the country specific laws.

Attrition rate

Of the 498 patients initially included, 342 (68.7%) completed according to the protocol. Of the 156 (31.3%) withdrawals, investigators withdrew 6, and 4 did not meet the inclusion criteria. The remaining 146 patients have decided by themselves to quit the study.

Measures

Met and unmet needs were assessed using the Camberwell Assessment of Needs (CAN) [23]. The CAN is a 22-item measure encompassing several domains of life that are potentially problematic for people suffering from mental illness. Domains of life are for example: “psychotic symptoms”, “accommodation”, “day time activities”, “intimate relationship”, but also “transport” or “money”. For each domain, the presence of needs and the coverage of needs by treatment are collected. Validity and reliability of the CAN are considered to be acceptable [23]. The construction of adequate summary indices is controversial [21, 36-38], but most studies rely on sum scores of met and unmet needs. The CAN allows for ratings by patients and ratings by professionals (e.g. therapists, caseworkers or research assistants). The Kappa coefficients for the agreement between ratings of professionals and patients are

between 0.18 – 0.53 [11, 12, 18, 33, 34, 38]. In the present study, sum scores of patient-rated met and unmet needs are used.

The Manchester Short Assessment of Quality of Life (MANSA) [25] is a widely used measure of quality of life encompassing 16 items, four questions about objective and twelve questions assessing subjective quality of life by asking patients about their satisfaction with several domains of life. Answers for subjective quality of life are on a 7 point scale ranging from 1=”could not be worse” to 7=”could not be better”. We used the mean of the 12 patient-rated subjective questions to calculate a quality of life score.

Other measures used in the present study were the PANSS (Positive And Negative Syndrome Scale [16]), the CDSS (Calgary Depression Scale for Schizophrenia [1]) measuring the level of depression in schizophrenia and the GAF (Global Assessment of Functioning [14]). The Hayward Scale [17] was used to assess compliance (one-item 7-points rating scale with higher scores suggesting better adherence), and prognosis was assessed using a 6-point scale ranging from 1=best to 6=bad.

The PANSS measures positive and negative symptoms of schizophrenia and general psychopathology. It is a 30 item structured interview scored by a trained rater, and lasts 30 – 40 minutes. Scores for positive and negative symptomatology, general psychopathology, and a total score are calculated.

The CDSS is a nine-item self-rating scale that assesses depression in schizophrenia with good reliability [2]. From all items, a total score (mean of ratings) is calculated. A

cut off of seven points refers to a specifity of 82% and a sensitivity of 85% for detecting major depressive episodes [1].

Socio demographic variables were assessed at baseline. All other measures were assessed at least at visit 1 (baseline) and visit 9 (after 12 months). Observer-rated measures were assessed by site-coordinators or co-investigators, e.g. psychiatrists (including trainees in psychiatry), research nurses, or psychologists.

Statistical analyses

To determine if values at baseline differed from values at the 12 months follow up, T-tests for paired samples and Wilcoxon-tests were used. All tests were calculated with PASW Statistics 18.0 for Windows.

Regression analysis

The dependent variable in regression analysis was the mean of the 12 items of the MANSA measuring subjective quality of life 12 months after the study begin. Independent variables were the basic socio demographic characteristics (gender, age, years of education, occupied at baseline), diagnosis, initial medication group (randomisation), psychosocial intervention (yes – no) and antipsychotic medication before the beginning of the study (yes – no); baseline quality of life (MANSA sum score), number of met and unmet needs, psychopathology (scores of the PANSS positive and negative symptoms, and the CDSS total mean score) and the global assessment of functioning (GAF) score. Additionally, compliance (Hayward scale) and prognosis were included. Only bivariate significant variables were selected for the models including several predictors simultaneously. Regression models were estimated using PASW Statistics 18.0 for Windows.

Structural Equation Models

Structural equation modelling (SEM) is the method of choice to study (longitudinal) interactions when predictor variables are closely interrelated (multicollinearity). To the best of our knowledge, there are no studies using SEM to inquire on the longitudinal association between needs and quality of life, with the exception of two studies using graphical chain modelling [27, 31].

We fitted two different structural equation models that both allow for a temporal sequence of unmet needs and change variables. The first aimed at replicating the results of the regression analysis to provide a base for subsequent models. The second model additionally included the number of changes from unmet needs to no needs and from unmet needs to met needs. Both models were developed using a stepwise deletion of paths. Primarily, a saturated model was fitted, with regression paths from all baseline variables to both change variables (met to unmet needs, met to no needs), and with regression paths from all variables to quality of life at follow up. The model further estimated correlations among baseline variables, and correlations among change variables. Starting from the saturated model, the paths with the lowest significance were omitted step by step, i.e. the model was run again after each deletion. The models were fitted using Mplus [22]. The model fit was assessed as suggested by Yu [40].

Results

From baseline to follow up at 12 months, 78.7% (263 of 334 completers with valid PANSS scores at both points in time) reached a 50% reduction on the PANSS total score, fulfilling the criterion for treatment success defined by Leucht et al. [20]. Major depressive episode (MDE) measured with the CDSS was diagnosed in 36.1% (123 of 341) at baseline; this was reduced to 3.5% (12 of 340) at 12 months. Most of the patients (completers) were in inpatient treatment setting at the beginning of the study (89.8%, 307 of 342) but only 4.7% (16 of 340) at follow-up. In sum, clinical improvement in the total sample was considerable.

Table 1 shows the descriptive statistics of quality of life and needs, clinical and social functioning. At baseline, study completers were more often female, and had more (met and unmet) needs, fewer psychosocial interventions, lower quality of life, and better compliance as well as prognosis. Fewer completers came from West Europe.

Table 1: Quality of life, needs, baseline socio-demographic data, clinical status and social functioning.

	Baseline total		Baseline completers		Drop outs		Difference drop outs - completers[7]
	mean ±SD / percent	N	mean ±SD / percent	N	mean ±SD / percent	N	P
age at baseline	25.98 ±5.55	(498)	26.05 ±5.64	(342)	25.83 ±5.38	(156)	0.618
gender (women)	40.2%	(200)	43.6%	(149)	32.7%	(51)	0.024
cultural region	-		-		-		0.000
West Europe	34.9%	(174)	28.9%	(99)	48.1%	(75)	-
East/Central Europe	51.4%	(256)	59.6%	(204)	33.3%	(52)	-
Israel	13.7%	(68)	11.4%	(39)	18.6%	(29)	-
occupation at baseline (yes)	46.6%	(231)	46.5%	(159)	46.8%	(72)	1.000
antipsychotic naïve at baseline	32.5%	(162)	30.7%	(105)	36.5%	(57)	0.216
years of education	12.46	(493)	12.58	(341)	12.17	(152)	0.140/0.181
medication							
…haloperidol	20.7%	(103)	19.9%	(68)	22.4%	(35)	0.227
…olanzapine	21.1%	(105)	24.0%	(82)	14.7%	(23)	-
…quetiapine	20.9%	(104)	20.5%	(70)	21.8%	(34)	-
…amisulpride	20.9%	(104)	20.2%	(69)	22.4%	(35)	-
…ziprasidone	16.5%	(82)	15.5%	(53)	18.6%	(29)	-
DSM-III-R diagnosis	-		-		-		0.603
Disorganized, catatonic, undifferentiated	8.4%	(42)	7.3%	(25)	10.9%	(17)	-
paranoid	44.8%	(223)	45.3%	(155)	43.6%	(68)	-
schizophreniform	39.8%	(198)	40.1%	(137)	39.1%	(61)	-
schizoaffective	7.0%	(35)	7.3%	(25)	6.4%	(10)	-
psychosocial intervention	14.1%	(70)	11.4%	(39)	19.9%	(31)	0.018
met needs patient, sum	2.59 ±2.57	(470)	2.78 ±2.73	(333)	2.15 ±2.06	(137)	0.007/0.034
unmet needs patient, sum	2.04 ±2.07	(470)	2.19 ±2.14	(333)	1.66 ±1.82	(137)	0.012/0.013
MANSA	4.04 ±0.92	(483)	3.98 ±0.90	(339)	4.19 ±0.96	(144)	0.023/0.022
GAF	40.03 ±13.51	(490)	40.72 ±13.50	(341)	38.46 ±13.44	(149)	0.087/0.107
PANSS total score	88.53 ±20.63	(487)	89.06 ±20.69	(340)	87.29 ±20.49	(147)	0.386/0.371
PANSS positive symptoms	23.13 ±6.19	(489)	23.36 ±6.17	(340)	22.59 ±6.23	(149)	0.205/0.138
PANSS negative symptoms	21.23 ±7.62	(489)	21.14 ±7.73	(341)	21.42 ±7.41	(148)	0.714/0.793
CDSS, sum score	5.07 ±4.87	(488)	5.27 ±4.88	(341)	4.62 ±4.84	(147)	0.176/0.140
prognosis by investigators	3.19 ±1.19	(495)	3.10 ±1.18	(342)	3.39 ±1.19	(153)	0.014/0.014
compliance (at 1 months)	5.57 ±1.20	(453)	5.66 ±1.16	(337)	5.30 ±1.29	(116)	0.006/0.006

[7] Significance of differences between baseline completers and dropouts were calculated for continuous/count/ordinal variables with t-tests (first p-value), to control for non-normal distributions with the Mann-Whitney-Test (second p-value) and with the chi-square tests for nominal variables.

Figure 1 expresses follow-up values as proportions of baseline values. Comparing change in different outcome measures, it becomes clear that changes were most pronounced in unmet needs rated by patients, positive symptoms (PANSS), and functioning (GAF-score).

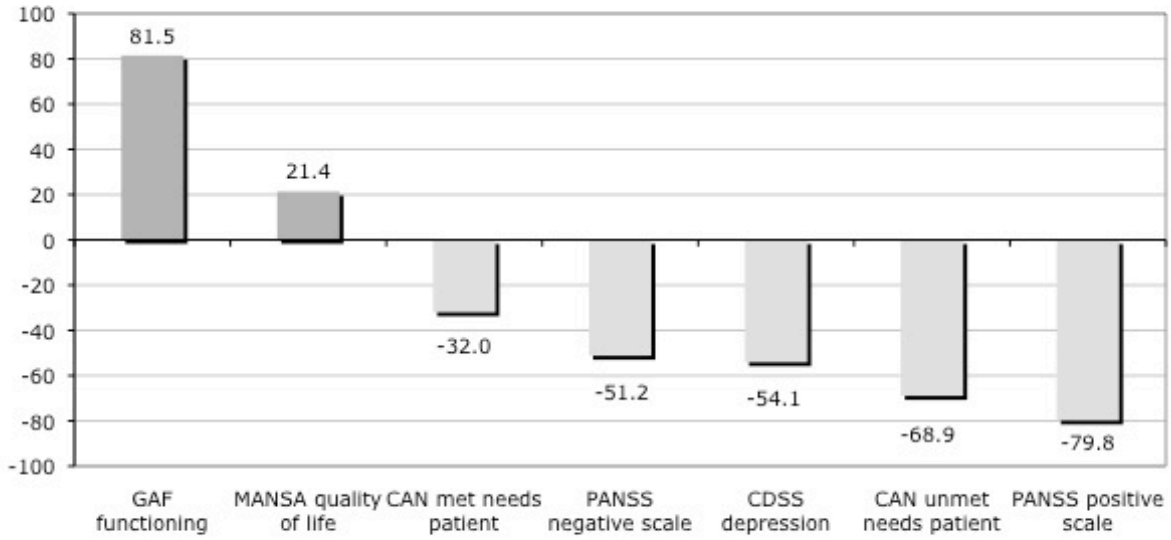

Fig 1: Difference between T1 scores and T9 scores expressed in percent of T1 values (vertical axis = difference scores). Sample of completers (N=326)

Predictors of Quality of Life using regression analysis

The baseline variables associated with quality of life at follow up were: Unmet needs, functioning (GAF), depression (CDSS), prognosis of patient, gender, age, current occupation and years of education. Associations with outcome quality of life changed in some time-dependent variables once baseline quality of life was included. Table 2 shows the multiple regression analysis results for all bivariate significant predictors of quality of life at follow up. In multivariate analyses, there model fit improved when baseline quality of life was included as a predictor of quality of life assessed at follow-up (Model 1 vs. Model 2 in Table 2). After including baseline quality of life as a

predictor, the baseline assessments of depression, gender and age remained significant predictors of quality of life at follow-up (Table 2, Models 2, 3). In contrast, the impact of unmet needs on quality of life was no longer significant. Interestingly, more depression at baseline was associated with higher quality of life at follow up. Younger female patients had higher quality of life at follow up.

Table 2: Regression model of MANSA sum score at follow up (dependent variable), and the following predictors: baseline clinical variables (Model 1)[8], baseline MANSA sum score and baseline clinical variables (Model 2)[9], baseline MANSA sum score, baseline clinical variables and socio-demographic variables (Model 3)[10] (N=326).

	B	Std	B std	T	P
Model 1	4.737	.317		14.949	.000
unmet needs	-.057	.023	-.149	-2.488	.013
CDSS score	.016	.010	.094	1.574	.117
GAF score	.006	.004	.097	1.576	.116
PANSS positive subscale	-.003	.008	-.022	-.369	.712
PANSS negative subscale	-.001	.006	-.013	-.216	.829
Model 2	3.659	.374		9.772	.000
unmet needs	-.034	.023	-.089	-1.507	.133
CDSS score	.026	.010	.158	2.672	.008
GAF score	.004	.004	.073	1.219	.224
PANSS positive subscale	-.003	.008	-.025	-.425	.671
PANSS negative subscale	-.001	.006	-.007	-.117	.907
MANSA total score	.259	.052	.286	4.988	.000
Model 3	4.399	.493		8.932	.000
unmet needs	-.032	.022	-.082	-1.408	.160
CDSS total score	.026	.010	.158	2.671	.008
GAF score	.003	.004	.055	.933	.351
PANSS positive subscale	-.004	.008	-.027	-.476	.634
PANSS negative subscale	.000	.006	-.001	-.025	.980
MANSA total score	.236	.052	.261	4.572	.000
patient age at randomisation	-.020	.008	-.135	-2.581	.010
gender	-.291	.087	-.176	-3.360	.001
education (in years)	.013	.016	.045	.808	.420
current occupation	.081	.094	.050	.869	.385
psychosocial intervention	-.229	.133	-.090	-1.723	.086
prognosis by investigators	-.036	.038	-.052	-.938	.349

[8] *R=.193 R-sq=.037 R-sq-k=.022*
[9] *R=.327 R-sq=.107 R-sq-k=.090*
[10] *R=.420 R-sq=.176 R-sq-k=.145*

Structural Equation Models

The first simple structural equation model led to nearly the same results as the regression model 2 in Table 2 (Figure 2). The longitudinal association between baseline unmet needs and follow up quality of life approached p=0.05. The second model (Figure 3) additionally included the number of changes of unmet needs to no needs or to met needs, and age and gender that were significant in regression model 3 (Table 2). Change from unmet needs to no needs was more strongly associated with quality of life than change from unmet needs to met needs (not significant). Fewer unmet needs, more depression, higher baseline quality of life, younger age and being female were associated with higher quality of life at follow up. Higher depression scores at baseline implicated more change to no needs, and, therefore, higher quality of life at follow up. Similarly, a higher level of positive symptoms was associated with more change from unmet needs to no needs. Younger female patients also had more unmet needs changing to no needs. Only depression and unmet needs were associated with the change to met needs (higher depression scores was associated with fewer changes to met needs).

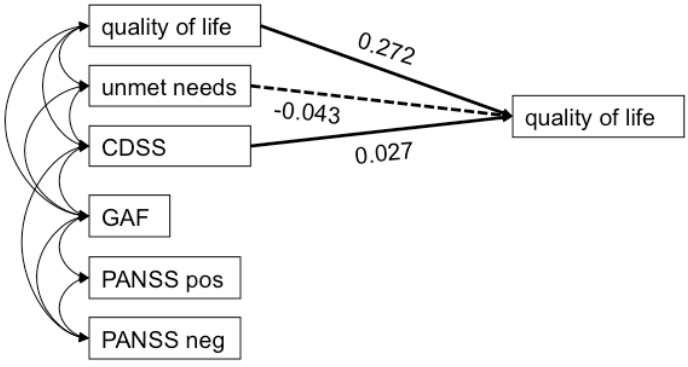

Fig 2: SEM model replicating regression model 2 (Table 2) (N=330)[11] [12]

[11] Only cross-lagged significant paths are depicted, even though cross sectional and autoregressive paths were estimated. Dashed line means nearly significant.

[12] Chi square value=5.671, df=8, P=0.6840; CFI=1.000, TLI=1.037; RMSEA=0.000, SRMR=0.030;Sample of completers with values on all variables (N=330).

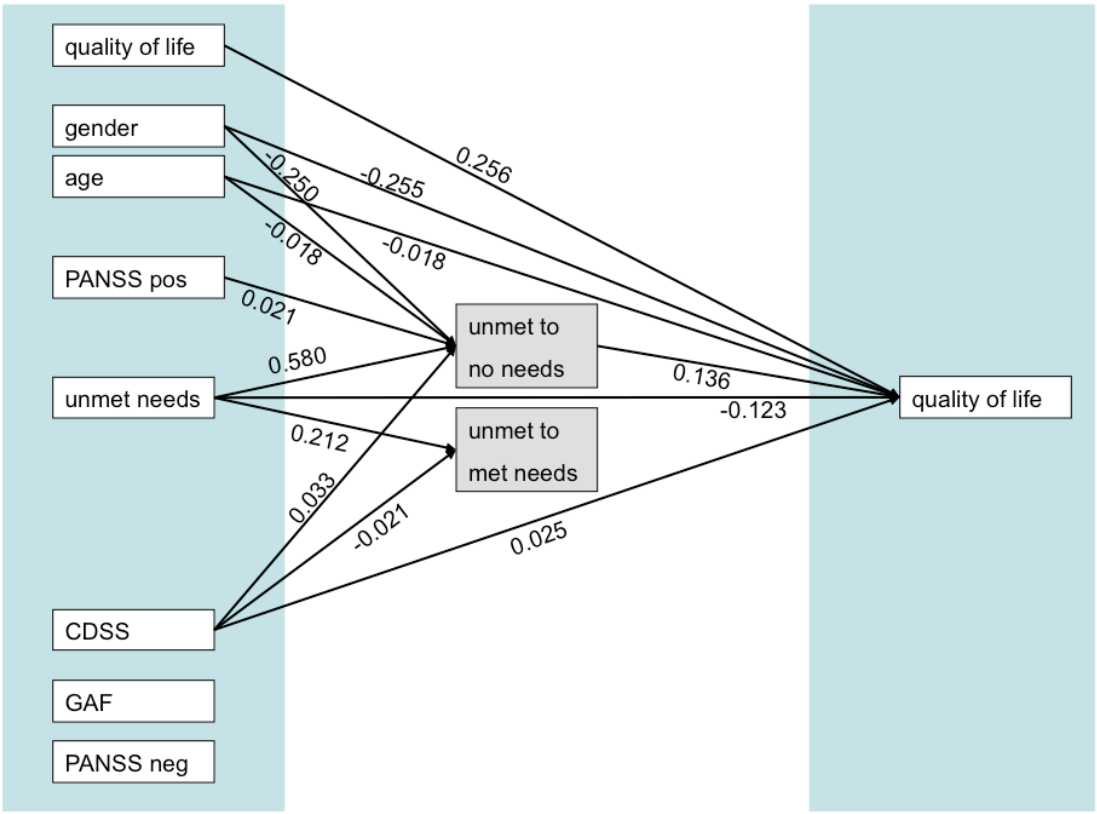

Fig 3: SEM model with same covariates as the model in Figure 2, but including age and gender, and differentiating between unmet needs that change to no needs and unmet needs that change to met needs (N=330)[13]

[13] Chi square value=15.037, df=18, P=0.6595; CFI=1.000, TLI=1.010; RMSEA=0.000, SRMR=0.026; Sample of completers with values on all variables (N=330).

Discussion

The present study aimed to explore the temporal interrelation between quality of life, unmet needs, and potentially associated clinical measures. It used a longitudinal sample of patients suffering from first episodes of schizophrenia. We believe there is no published study of a comparably homogenous sample at the onset of illness. Not surprisingly, there were marked improvements in all social and psychopathological outcome indicators over time. While previous studies [30, 31] found a longitudinal interrelation between needs and quality of life, this finding was not clearly confirmed by our study. We used statistical techniques that allowed for a differentiation between needs and the change from unmet needs to no needs. In this sample of first episode patients, the change of unmet needs to no needs had a stronger impact on quality of life than needs being met. This is self-evident but indicates that the longitudinal association between the two constructs depends not on the mere reduction of, but on the specification what happened to the unmet needs.

Needs and quality of life

Our results suggest that the interrelation between quality of life and unmet needs is due to cross-sectional rather than longitudinal association in first episode patients. The weak evidence for a longitudinal association challenges the assumption of a causal interrelation of unmet needs and quality of life. Using conventional regression, the association between earlier unmet needs and subsequent quality of life found by previous studies was confirmed only if baseline quality of life was omitted. With the SEM modelling technique, the longitudinal impact of earlier unmet needs on subsequent quality of life was not confirmed unless meeting needs was differentiated from needs that changed to no needs during the study. One would expect that any

non-random, strong effect would have shown up unequivocally in both longitudinal methodological approaches used. There are not many longitudinal studies with which to compare our results. Slade et al. [31] found a relation of earlier unmet needs with later quality of life. Another study [30] using random coefficient models found an effect of change in unmet needs as well as mean level of unmet need on quality of life. Earlier longitudinal studies testing the impact of psychopathology and functioning but not needs on quality of life proposed weak or no predictors of subjective quality of life using graphical chain modelling [27] or regression analysis [28]. Overall, most available studies confirm a longitudinal effect of unmet needs on quality of life. Met needs had an even more inconsistent and weaker association with quality of life in our study. No study found that more met needs were interrelated with higher quality of life. Met needs appear to have the implication of something missing, despite them being met. In other words, met needs are better than unmet needs, but cannot be equated with health or wellbeing. This is in line with our finding that quality of life was more positively influenced by unmet needs that diminished than by unmet needs that were met. Therefore, the reduction of unmet needs does not enhance quality of life in any case. Meeting a need means that patients are still in need of help in this area of life. This result is intuitively compelling. But it sheds another light on what is measured when assessing needs, namely, a conglomerate of different aspects of illness, treatment and recovery. Granted that treatment implies the meeting of patient's needs, treatment only has a relatively marginal influence on the improving of quality of life in our sample. But what has caused the change to no needs that had a stronger impact on quality of life? The EUFEST trial describes a homogenous sample moving through very different stages of schizophrenia. At baseline, patients were in the acute phase, and nearly all in hospital care. At the 12-month follow up, most were outpatients and in remission, or stabilization phase of their illness. Additionally,

patients suffering from first episode schizophrenia have a more favourable treatment response than more chronically ill patients [13]. This might help to explain why there were so many needs for care which changed to no needs.

One important question is how unmet needs could be changed to no needs by treatment? Is there a direct way from unmet needs to no needs? Is the change to no needs also a result of treatment, or has this to be understood as a spontaneous remission? Those questions are difficult to answer, but we recommend that results based on treatment needs should be interpreted only in combination with other measures that validate different aspects of progress.

There are several explanations for the unstable longitudinal interrelation of unmet needs and quality of life found in this study. A previous study compared first admitted and long term hospitalized patients. It detected stronger associations between needs and quality of life in the long term hospitalized sample [26]. As our patients were all in early stages of schizophrenia, this could explain the missing associations. In early stages of schizophrenia there is considerable change; improving patients may be more easily influenced in both positive and negative directions. Other non-treatment factors may outweigh treatment factors at the beginning of an illness. Longer established schizophrenia is associated with an increasing reliance of patients on professionals and health services. The reduced importance of treatment systems in our early sample may explain some of the relatively low impact of treatment needs on quality of life in our sample. The instability of the regression models may also be due to the different situation (e.g. hospital and outpatient care) of patients at baseline and at follow up.

The vast number of possible influences on the relation between needs and quality of life in mind helps explain the inconsistent results in different studies. Further influences are whether routine outcome data or research data is used, which diagnostic groups are included and in which stage of illness and setting (in hospital vs. outpatients) and lastly treatment received. In addition, there are several quality of life instruments in use, and needs can be rated by therapists, research assistants or the patients themselves.

Other predictors of quality of life

Longitudinal studies of the interrelation of unmet needs with other outcome measures than quality of life are sparse and provided inconsistent results. An advantage of the model used is that it explains the change in quality of life. By including baseline quality of life, the path from baseline to follow up levels of quality of life represents the values remaining stable. The other paths to quality of life explain change. In this population of patients, new to their illness, depression was longitudinally more clearly interrelated with quality of life than positive and negative symptoms and unmet needs. Patients with more depression at baseline had more changes to no needs, and therefore, a better quality of life at follow up. The diminishing of unmet needs was, in addition to higher depression scores, related to more positive symptoms at baseline. Meeting needs was predicted by lower depression scores, but not by positive symptoms. There must be patients with marked symptom load at baseline who experience alleviation in terms of diminishing need for care for symptoms. This in turn influences their subjective quality of life. Interestingly there was no direct effect of positive symptoms, but patients with more depression at baseline tended to have a better quality of life at follow up. Functioning was not associated with quality of life. This is in line with the finding that social functioning and quality of life are

independent in schizophrenic patients living in the community [6]. Female gender and younger age consistently influenced change and quality of life positively. For further research it would be interesting to know more about those complex interrelations.

Future research

In sum, there is a need for research clearing the following points: The differential impact of needs that disappear and need that are met on quality of life should be replicated using more measurements and with different patient groups. Treatment research is needed to study the processes that lead to change in needs, and to find out what causes needs to disappear. Experimental studies are necessary to determine the direction of causality.

Limitations

Naturalistic studies as ours are limited in their capacity to determine causal effects. If the conditions (independent variables) are not manipulated experimentally, causal hypotheses cannot be tested with certainty. No definite discrimination between correlation and causality is possible. Results of this study should be interpreted as a first step in proving that the change from unmet to met needs leads to an improvement of quality of life.

An impediment on the validity of results was drop out. This is a problem of most longitudinal studies. Moreover there was a difference between patients who completed the study and patients who dropped out for a variety of reasons. Adherent patients were those with more needs, higher quality of life, and better compliance as well as prognosis at baseline. Strictly speaking, our results are valid only for first episode patients with higher baseline quality of life. We refrained from using imputation of missing data, because this does not reduce the risk of biased results when only two measurements are available. More assessments would allow for

better imputation solutions, or for calculating random coefficient models/multilevel models that use all available information.

Finally, the sample of the EUFEST study might not represent the average first episode patient, as patients who signed informed consent might differ from patients who did not, all patients were in inpatient treatment, and centres were not selected randomly.

Conclusions

This study questions the generally accepted assumption that meeting needs enhances quality of life. During the transition from acute to more stable phases of illness, unmet needs are associated with outcome quality of life only when they have diminished until the outcome assessment. For further research, it is important to differentiate meeting unmet needs and unmet needs that change to no needs.

Acknowledgments

The analyses presented in this paper were done without funding. The EUFEST-trial was funded by the European Group for Research in Schizophrenia (EGRIS) with grants from AstraZeneca, Pfizer, and Sanofi-Aventis.

We thank all the patients who took part in the study.

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